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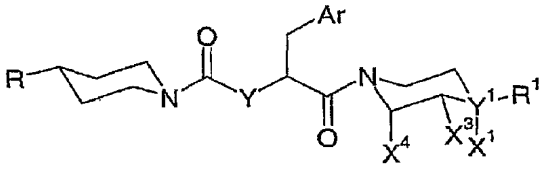
(54) NOUVEAUX ACIDES CARBOXYLIQUES ET LEURS ESTERS, COMPOSITIONS PHARMACEUTIQUES CONTENANT CES COMPOSES ET PROCEDE DE PREPARATION CONNEXE

(54) NEW CARBOXYLIC ACIDS AND THE ESTERS THEREOF, PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS AND PROCESSES FOR THE PREPARATION THEREOF

(57)

The invention relates to carboxylic acids and esters of a general formula (I), wherein Ar, R, R1, X1, X3, X4, Y and Y1 have a definition given in a claim 1. Said invention also relates to tautomers, the enantiomers, mixtures and salts thereof, in particular to physiologically compatible salts containing organic or inorganic acids or bases, drugs containing said compounds using them as CGRT antagonists for treating a headache and to method for the production and use thereof for producing and cleaning antibodies and as labelled compounds for RIA and ELISA biological dosages and, finally as auxiliary diagnostics or analytics for neutrotransmitters.



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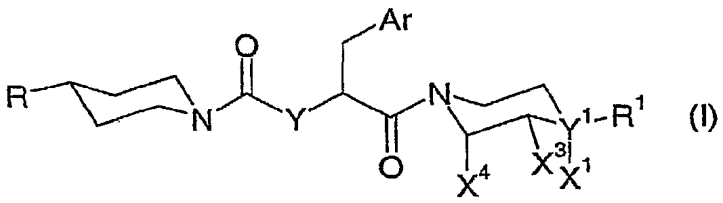
(54) Titre : DERIVES DE N- (1-BENZYL-2-OXO-2- (1-PIPERAZINYL) ETHYLE) -1-PIPERIDINE-CARBOXAMIDE ET COMPOSES APPARENTES UTILISES COMME ANTAGONISTES DE CGRP ET DESTINES AU TRAITEMENT DES MAUX DE TETE

(54) Title: N- (1-BENZYL-2-OXO-2- (1-PIPERAZINYL) ETHYL) -1-PIPERIDINCARBOXAMID-DERIVATIVES AND RELATED COMPOUNDS USE AS CGRP-ANTAGONISTS FOR TREATING A HEADACHE



(I)

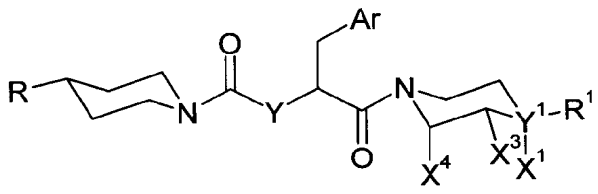
(57) Abrégé/Abstract:
The invention relates to carboxylic acids and esters of a general formula (I), wherein Ar, R, R^{1}, X^{1}, X^{3}, X^{4}, Y and Y^{1} have a definition given in a claim 1. Said invention also relates to tautomers, the enantiomers, mixtures and salts thereof, in particular to physiologically compatible salts containing organic or inorganic acids or bases, drugs containing said compounds using them as CGRT antagonists for treating a headache and to method for the production and use thereof for producing and cleaning antibodies and as labelled compounds for RIA and ELISA biological dosages and, finally as auxiliary diagnostics or analytics for neutrotransmitters.

(21) 2 513 132
(13) A1

(72) **Inventeurs(suite)/Inventors(continued)**: RUDOLF, KLAUS, DE; SCHINDLER, MARCUS, DE; STENKAMP, DIRK, DE

Abstract

The present invention relates to carboxylic acids and esters of general formula



, (I)

wherein Ar, R, R^1, X^1, X^3, X^4, Y and Y^1 are defined as in claim 1, the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, pharmaceutical compositions containing these compounds, the use thereof and processes for the preparation thereof, as well as the use thereof for the production and purification of antibodies and as labelled compounds in RIA and ELISA assays and as diagnostic or analytical aids in neurotransmitter research.

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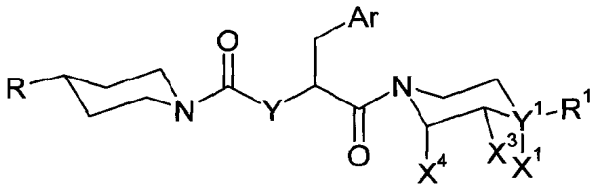
New carboxylic acids and the esters thereof, pharmaceutical compositions containing these compounds and processes for the preparation thereof

The present invention relates to new carboxylic acids and the esters thereof of general formula



, (I)

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, pharmaceutical compositions containing these compounds, the use thereof and processes for the preparation thereof.

In the above general formula I

R denotes a monounsaturated 5- to 7-membered diaza, triaza or *S,S*-dioxido-thiadiaza heterocycle,

while the above-mentioned heterocycles are linked via a nitrogen atom and

are characterised by a carbonyl group or sulphonyl group each flanked by two nitrogen atoms,

may be substituted at one or at two carbon atoms by an alkyl, phenyl, pyridinyl, thienyl or 1,3-thiazolyl group, while the substituents may be identical or different,

and the double bond of one of the above-mentioned unsaturated

heterocycles may be fused to a benzene, pyridine or quinoline ring,

while the phenyl, pyridinyl, thienyl, or 1,3-thiazolyl groups contained in R as well as benzo-, pyrido- and quinolino-fused heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl, alkoxy, nitro, alkylthio, alkylsulphinyl, alkylsulphonyl, alkylsulphonylamino, phenyl, trifluoromethyl, alkoxycarbonyl, carboxy, dialkylamino, hydroxy, amino, acetylamino, propionylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, methylenedioxy, aminocarbonylamino, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, while the substituents may be identical or different,

Ar denotes a phenyl, 1-naphthyl, 2-naphthyl, tetrahydro-1-naphthyl, tetrahydro-2-naphthyl, 1*H*-indol-3-yl, 1-methyl-1*H*-indol-3-yl, 1-formyl-1*H*-indol-3-yl, 4-imidazolyl, 1-methyl-4-imidazolyl, 2-thienyl, 3-thienyl, thiazolyl, 1*H*-indazol-3-yl, 1-methyl-1*H*-indazol-3-yl, benzo[b]furyl, 2,3-dihydrobenzo[b]furyl, benzo[b]thienyl, pyridinyl, quinolinyl or isoquinolinyl group,

while the above-mentioned aromatic and heteroaromatic groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, phenylalkyl groups, alkenyl, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, carboxy, dialkylamino, nitro, hydroxy, amino, alkylamino, acetylamino, propionylamino, methylsulphonyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups and the substituents may be identical or different,

Y denotes the methylene or the -NH- group,

Y^1 denotes the carbon or the nitrogen atom,

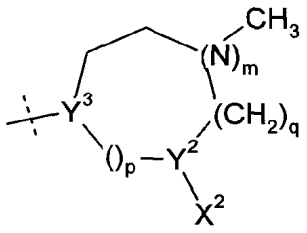
X^1 denotes the pair of free electrons, if Y^1 denotes the nitrogen atom, or, if Y^1 is the carbon atom, denotes a hydrogen atom or a carboxylic acid group optionally esterified with a lower aliphatic alcohol,

X^3 and X^4 in each case denote the hydrogen atom or the carboxylic acid group optionally esterified with a lower aliphatic alcohol,

with the proviso that at least one but also not more than one of the groups X^1, X^2, X^3 or X^4 contains an optionally esterified carboxylic acid function,

and

R^1 denotes a group of general formula



, (IIa)

wherein

Y^2 denotes the carbon or, if m assumes the value 0, also the nitrogen atom,

Y^3, which is always different from Y^1, denotes the carbon or nitrogen atom,

X^2 denotes a group of general formula

$$CH_2CO_2R^2 \quad , (III)$$

wherein

R^2 denotes the hydrogen atom or a C_{1-5}-alkyl group,

or, if Y^2 is the carbon atom, it may also denote the hydrogen atom or the carboxylic acid group optionally esterified with a lower aliphatic alcohol,

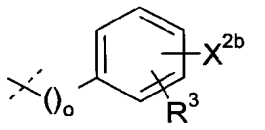
m denotes the numbers 0 or 1,

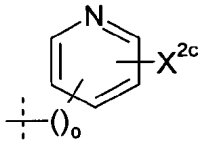
p denotes the numbers 0, 1, 2 or 3 and

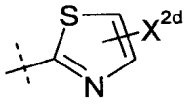
q denotes the numbers 0, 1 or 2,

while the sum of m, p and q may assume the values 1, 2 or 3,

or one of the groups (IIb), (IIc) or (IId)


(IIb),


(IIc), or


, (IId)

wherein

X^{2b}, X^{2c} and X^{2d} each denote the hydrogen atom or a carboxylic acid group optionally esterified with a lower aliphatic alcohol,

o denotes the numbers 0, 1, 2 or 3 and

R^3 denotes the hydrogen atom, the fluorine, chlorine or bromine atom, an alkyl, alkoxy, nitro, trifluoromethyl, hydroxy, amino, acetylamino,

aminocarbonyl, acetyl or cyano group,

while, unless otherwise stated, the above-mentioned alkyl groups or the alkyl groups contained in the above-mentioned groups contain 1 to 5 carbon atoms and may be straight-chain or branched.

The present invention relates to racemates, if the compounds of general formula I have only one chiral element. The application also includes, however, the individual diastereomeric pairs of antipodes or the mixtures thereof which are obtained when there is more than one chiral element in the compounds of general formula I, as well as the individual optically active enantiomers of which the above-mentioned racemates are composed.

The compounds of general formula I have valuable pharmacological properties, which are based on their selective CGRP-antagonistic properties. The invention further relates to pharmaceutical compositions containing these compounds, the use thereof and the preparation thereof.

Preferred compounds of the above general formula I are those wherein

R denotes a monounsaturated 5- to 7-membered diaza, triaza or *S,S*-dioxido-thiadiaza heterocycle,

while the above-mentioned heterocycles are linked via a nitrogen atom and

are characterised by a carbonyl group or sulphonyl group in each case flanked by two nitrogen atoms,

may be substituted at a carbon atom by a phenyl, pyridinyl, thienyl or 1,3-thiazolyl group,

and the double bond of one of the above-mentioned unsaturated heterocycles may be fused to a benzene, pyridine or quinoline ring,

while the phenyl, pyridinyl, thienyl, or 1,3-thiazolyl groups contained in R as well as benzo-, pyrido- and quinolino-fused heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl, alkoxy, trifluoromethyl, amino, cyano or acetylamino groups, while the substituents may be identical or different,

Ar denotes a phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl or 2,3-dihydrobenzo[b]fur-5-yl group,

while the above-mentioned aromatic and heteroaromatic groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, by alkyl groups, alkoxy, trifluoromethyl, nitro, hydroxy, amino, aminocarbonyl, acetyl or cyano groups and the substituents may be identical or different,

Y denotes the methylene or the -NH- group,

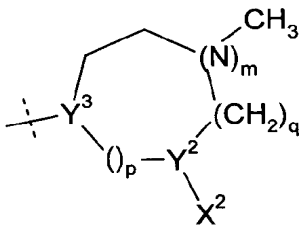
Y^1 denotes the carbon or the nitrogen atom,

X^1 denotes a pair of free electrons, if Y^1 denotes the nitrogen atom, or, if Y^1 is the carbon atom, the hydrogen atom or the carboxylic acid group optionally esterified with a lower aliphatic alcohol,

X^3 and X^4 each denote the hydrogen atom or the carboxylic acid group optionally esterified with a lower aliphatic alcohol,

with the proviso that at least one but also not more than one of the groups X^1, X^2, X^3 or X^4 contains an optionally esterified carboxylic acid function, and

R^1 denotes a group of general formula



, (IIa)

wherein

Y^2 denotes the carbon atom or, if m assumes the value 0, may also denote the nitrogen atom,

Y^3, which is always different from Y^1, denotes the carbon or the nitrogen atom,

X^2 denotes a group of general formula

$$CH_2CO_2R^2 \quad , (III)$$

wherein

R^2 denotes the hydrogen atom or a C_{1-5}-alkyl group,

or, if Y^2 is the carbon atom, also denotes the hydrogen atom or the carboxylic acid group optionally esterified with a lower aliphatic alcohol,

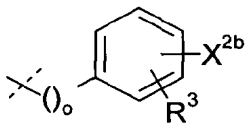
m denotes the numbers 0 or 1,

p denotes the numbers 0, 1 or 2 and

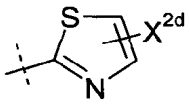
q denotes the numbers 0, 1 or 2,

while the sum of m, p and q may assume the values 1 or 2,

or one of the groups



(IIb), or



, (IId)

wherein

X^{2b} and X^{2d} each denote the hydrogen atom or the carboxylic acid group optionally esterified with a lower aliphatic alcohol,

o denotes the numbers 0, 1, 2 or 3 and

R^3 denotes the hydrogen atom, the fluorine, chlorine or bromine atom, a methyl, methoxy, nitro, trifluoromethyl or cyano group,

while, unless otherwise stated, the above-mentioned alkyl groups or the alkyl groups contained in the above-mentioned groups contain 1 to 4 carbon atoms and may be branched or unbranched,

the tautomers, the diastereomers, the enantiomers and the salts thereof.

Particularly preferred compounds of the above general formula I are those wherein

R denotes a monounsaturated 5- to 7-membered diaza, triaza or *S,S*-dioxido-thiadiaza heterocycle,

while the above-mentioned heterocycles are linked via a nitrogen atom and

are characterised by a carbonyl group or sulphonyl group each flanked by two nitrogen atoms,

may be substituted at a carbon atom by a phenyl group,

and the double bond of one of the above-mentioned unsaturated heterocycles may be fused to a benzene, pyridine or quinoline ring,

while the phenyl groups contained in R as well as benzo-, pyrido- and quinolino-fused heterocycles may additionally be mono- or disubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, by methyl, methoxy, trifluoromethyl, or cyano groups, while the substituents may be identical or different,

Ar denotes a phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl or 2,3-dihydrobenzo[b]fur-5-yl group,

while the above-mentioned aromatic and heteroaromatic groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, by methyl, methoxy, trifluoromethyl, hydroxy or amino groups and the substituents may be identical or different,

Y denotes the methylene or -NH- group,

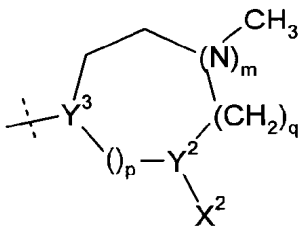
Y^1 denotes the carbon or nitrogen atom,

X^1 denotes a pair of free electrons, if Y^1 denotes the nitrogen atom, or, if Y^1 is the carbon atom, the hydrogen atom or the carboxylic acid group optionally esterified with methanol or ethanol,

X^3 and X^4 each denote the hydrogen atom or the carboxylic acid group optionally esterified with methanol or ethanol,

with the proviso that at least one but also not more than one of the groups X^1, X^2, X^3 or X^4 contains an optionally esterified carboxylic acid function, and

R^1 denotes a group of general formula



, (IIa)

wherein

Y^2 denotes the carbon or, if m assumes the value 0, also denotes the nitrogen atom,

Y^3, which is always different from Y^1, denotes the carbon or the nitrogen atom,

X^2 denotes a group of general formula

$$CH_2CO_2R^2 \quad , (III)$$

wherein

R^2 denotes the hydrogen atom or a straight-chain or branched C_{1-4}-alkyl group,

or, if Y^2 is the carbon atom, also denotes the hydrogen atom or the carboxylic acid group optionally esterified with methanol or ethanol,

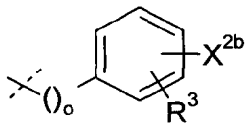
m denotes the numbers 0 or 1,

p denotes the numbers 0, 1 or 2 and

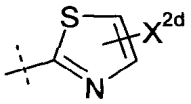
q denotes the numbers 0, 1 or 2,

while the sum of m, p and q may assume the values 1 or 2,

or one of the groups



(IIb), or



, (IId)

wherein

X^{2b} and X^{2d} each denote the hydrogen atom or the carboxylic acid group optionally esterified with methanol or ethanol,

o denotes the numbers 0, 1 or 2 and

R^3 denotes the hydrogen atom, the fluorine, chlorine or bromine atom, a methyl, methoxy or trifluoromethyl group,

while, unless otherwise stated, the above-mentioned alkyl groups or the alkyl groups contained in the above-mentioned groups contain 1 to 4 carbon atoms and may be straight-chain or branched,

the tautomers, the diastereomers, the enantiomers and the salts thereof.

Most particularly preferred compounds of the above general formula (I) are those wherein

R denotes the 3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl, 2,4-dihydro-5-phenyl-3(3*H*)-oxo-1,2,4-triazol-2-yl, 1,3-dihydro-2(2*H*)-oxoimidazo[4,5-c]quinolin-3-yl, 2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl, 3,4-dihydro-2(1*H*)-oxopyrido[3,4-d]pyrimidin-3-yl or 3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl group,

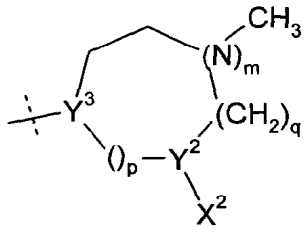
Ar denotes the 3,5-dibromo-4-hydroxyphenyl, 4-amino-3,5-dibromophenyl, 4-bromo-3,5-dimethylphenyl, 3,5-dichloro-4-methylphenyl, 3,4-dibromophenyl, 3-bromo-4,5-dimethylphenyl, 3,5-dibromo-4-methylphenyl, 3-chloro-4-methylphenyl, 3,4-difluorophenyl, 4-hydroxyphenyl, 1-naphthyl, 3,5-dibromo-4-fluorophenyl, 3,5-bis-(trifluoromethyl)-phenyl, 3,4,5-trimethylphenyl, 3-(trifluoromethyl)-phenyl, 3,5-dimethyl-4-methoxyphenyl, 4-amino-3,5-dichlorophenyl, 2,4-bis-(trifluoromethyl)-phenyl, 3,4,5-tribromophenyl, 3,4-dimethoxyphenyl, 3,4-dichlorophenyl, 4-bromo-3,5-dichlorophenyl, 2-naphthyl, 2,3-dihydrobenzo[b]fur-5-yl, 1,2,3,4-tetrahydro-1-naphthyl or 2,3-dichlorophenyl group,

Y denotes the methylene or the -NH- group,

Y^1 denotes the carbon or the nitrogen atom,

X^1 denotes a pair of free electrons, if Y^1 denotes the nitrogen atom, or, if Y^1 is the carbon atom, the hydrogen atom, the carboxylic acid or the methoxy-carbonyl group and

R^1 denotes a group of general formula



, (IIa)

wherein

Y^2 denotes the carbon atom or, if m assumes the value 0, also the nitrogen atom,

Y^3, which is always different from Y^1, denotes the carbon or the nitrogen atom,

X^2 denotes a group of general formula

$$CH_2CO_2R^2 \quad , (III)$$

wherein

R^2 denotes the hydrogen atom or a straight-chain or branched C_{1-4}-alkyl group,

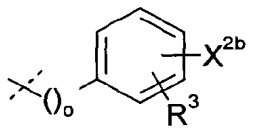
or, if Y^2 is the carbon atom, also denotes the hydrogen atom or the carboxylic acid group optionally esterified with methanol or ethanol,

m denotes the numbers 0 or 1,

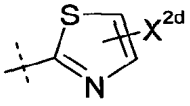
p and q in each case denotes the numbers 0, 1 or 2,

while the sum of m, p and q may assume the values 1 or 2,

or one of the groups



(IIb), or



, (IId)

wherein

X^{2b} denotes the hydrogen atom or the carboxylic acid group optionally esterified with methanol or ethanol,

X^{2d} denotes the hydrogen atom or the carboxylic acid group optionally esterified with methanol,

o denotes the numbers 0, 1 or 2 and

R^3 denotes the hydrogen atom or the trifluoromethyl group,

while, unless otherwise stated, the above-mentioned alkyl groups or the alkyl groups contained in the above-mentioned groups contain 1 to 4 carbon atoms and may be straight-chain or branched,

the tautomers, the diastereomers, the enantiomers and the salts thereof.

The following are mentioned as examples of particularly preferred compounds:

(1) ethyl 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-1-piperazineacetate,

(2) 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-1-piperazineacetic acid,

(3) 1,1-dimethylethyl 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-1-piperidineacetate,

(4) 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-1-piperidineacetic acid,

(5) methyl 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-[1,4']bipiperidinyl-4-acetate,

(6) 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-[1,4']bipiperidinyl-4-acetic acid,

(7) ethyl *endo*-4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-

cyclohexanecarboxylate,

(8) *endo*-4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-cyclohexanecarboxylic acid,

(9) ethyl *exo*-4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-cyclohexanecarboxylate,

(10) *exo*-4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-cyclohexanecarboxylic acid,

(11) ethyl 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-1-piperidineacetate,

(12) methyl 1'-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-[1,4']bipiperidinyl-4-acetate,

(13) 1'-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-[1,4']bipiperidinyl-4-acetic acid,

(14) ethyl 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-1-piperidineacetate,

(15) ethyl 4-{1-[4-bromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3,5-dimethyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(16) ethyl 4-{1-[3,5-dichloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-

piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(17) ethyl 4-{1-[3,4-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(18) ethyl 4-{1-[3-bromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4,5-dimethyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(19) ethyl 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(20) ethyl 4-{1-[3-chloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(21) ethyl 4-{4-[4-bromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3,5-dimethyl-D,L-phenylalanyl]-1-piperazinyl}-1-piperidineacetate,

(22) 4-{1-[4-bromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3,5-dimethyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(23) 4-{1-[3,5-dichloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(24) 4-{1-[3,4-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(25) 4-{1-[3-bromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4,5-dimethyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(26) 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(27) 4-{1-[3-chloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(28) 4-{4-[4-bromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3,5-dimethyl-D,L-phenylalanyl]-1-piperazinyl}-1-piperidineacetic acid,

(29) 1,1-dimethylethyl 4-{1-[3,4-difluoro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(30) methyl 1'-[*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-[1,4']bipiperidinyl-4-acetate,

(31) ethyl 4-{1-[*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-1-piperazineacetate,

(32) ethyl (*R,S*)-4-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetate,

(33) methyl 1-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-(*S*)-pyrrolidine-2-carboxylate,

(34) methyl 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-(*S*)-pyrrolidine-2-carboxylate,

(35) 1-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-(*S*)-pyrrolidine-2-carboxylic acid,

(36) 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-(*S*)-pyrrolidine-2-carboxylic acid,

(37) methyl 1-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-(*R*)-pyrrolidine-2-carboxylate,

(38) methyl 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-(*R*)-pyrrolidine-2-carboxylate,

(39) 1-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-(*R*)-pyrrolidine-2-carboxylic acid,

(40) 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-(*R*)-pyrrolidine-2-carboxylic acid,

(41) methyl 1'-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-(*R*)-[1,4']bipiperidinyl-2-carboxylate,

(42) methyl 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-

piperidinyl]carbonyl]-D-tyrosyl]-(*R*)-[1,4']bipiperidinyl-2-carboxylate,

(43) methyl 1'-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-(*S*)-[1,4']bipiperidinyl-2-carboxylate,

(44) methyl 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-(*S*)-[1,4']bipiperidinyl-2-carboxylate,

(45) 1'-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-(*R*)-[1,4']bipiperidinyl-2-carboxylic acid,

(46) 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-(*R*)-[1,4']bipiperidinyl-2-carboxylic acid,

(47) 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-(*S*)-[1,4']bipiperidinyl-2-carboxylic acid,

(48) 1'-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-(*S*)-[1,4']bipiperidinyl-2-carboxylic acid,

(49) methyl 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-[1,4']bipiperidinyl-4'-carboxylate,

(50) methyl 1'-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-[1,4']bipiperidinyl-4'-carboxylate,

(51) 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-[1,4']bipiperidinyl-4'-carboxylic acid,

(52) 1'-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-

piperidinyl]carbonyl]-D-phenylalanyl]-[1,4']bipiperidinyl-4'-carboxylic acid,

(53) 1'-[*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-[1,4']bipiperidinyl-4-acetic acid,

(54) 4-{1-[*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-1-piperazineacetic acid,

(55) ethyl 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-benzoate,

(56) ethyl 3-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-benzoate,

(57) methyl 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-benzoate,

(58) ethyl 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinylmethyl}-benzoate,

(59) ethyl 4-{2-[1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl]-ethyl}-benzoate,

(60) methyl 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-3-(trifluoromethyl)-benzoate,

(61) methyl 3-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-benzoate,

(62) ethyl 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-benzoate,

(63) ethyl 3-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-benzoate,

(64) methyl 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-benzoate,

(65) methyl 4-{2-[1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl]-ethyl}-benzoate,

(66) methyl 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-3-(trifluoromethyl)-benzoate,

(67) methyl 3-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-benzoate,

(68) 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-benzoic acid,

(69) 3-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-benzoic acid,

(70) 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-benzoic acid,

(71) 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinylmethyl}-benzoic acid,

(72) 4-{2-[1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-

piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl]-ethyl}-benzoic acid,

(73) 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-3-(trifluoromethyl)-benzoic acid,

(74) 3-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-benzoic acid,

(75) 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-benzoic acid,

(76) 3-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-benzoic acid,

(77) 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-terahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-benzoic acid,

(78) 4-{2-[1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl]-ethyl}-benzoic acid,

(79) 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-3-(trifluoromethyl)-benzoic acid,

(80) 3-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-benzoic acid,

(81) ethyl 4-{1-[3-(1-naphthyl)-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-

benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-alanyl]-4-piperidinyl}-1-piperazineacetate,

(82) 4-{1-[3-(1-naphthyl)-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-alanyl]-4-piperidinyl}-1-piperazineacetic acid,

(83) methyl 2-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-5-thiazolecarboxylate,

(84) methyl 2-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-4-thiazolecarboxylate,

(85) 2-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-5-thiazolecarboxylic acid,

(86) 2-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-4-thiazolecarboxylic acid,

(87) methyl 2-{4-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-4-thiazolecarboxylate,

(88) methyl 2-{4-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-5-thiazolecarboxylate,

(89) 2-{4-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-4-thiazolecarboxylic acid,

(90) 2-{4-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-5-thiazolecarboxylic acid,

(91) 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-1-piperidineacetic acid,

(92) 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-1-piperidineacetic acid,

(93) 1,1-dimethylethyl 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(94) 1,1-dimethylethyl 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(95) ethyl 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(96) ethyl 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(97) 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(98) 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(99) (*R,S*)-4-{1-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-

2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(100) (*R,S*)-4-{1-[2-[(3,5-dibromo-4-fluorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(101) (*R,S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxopyrido[3,4-d]pyrimidin-3-yl)-1-piperidinyl]-2-[(1-naphthyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(102) (*R,S*)-4-{1-[2-[[3,5-bis-(trifluoromethyl)-phenyl]methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(103) (*R,S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4,5-trimethylphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(104) (*R,S*)-4-{1-[2-[(3-bromo-4,5-dimethylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(105) (*R,S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(trifluoromethyl)-phenyl]methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(106) (*R,S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-methoxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(107) (*R,S*)-4-{1-[2-[(4-amino-3,5-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(108) (*R*,*S*)-4-{1-[2-[[2,4-bis-(trifluoromethyl)-phenyl]methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(109) (*R*,*S*)-4-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(110) (*R*,*S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4,5-tribromophenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(111) (*R*,*S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dimethoxyphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(112) (*R*,*S*)-4-{1-[2-[(3,4-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(113) (*R*,*S*)-4-{1-[2-[(4-bromo-3,5-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(114) (*R*,*S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(2-naphthyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(115) (*R*,*S*)-4-{1-[2-[(2,3-dihydrobenzo[b]fur-5-yl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(116) (*R*,*S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-

2-[(1,2,3,4-tetrahydro-1-naphthyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(117) (*R,S*)-4-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(118) (*R,S*)-4-{1-[2-[(2,3-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(119) ethyl (*R,S*)-4-{1-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetate,

(120) (*R,S*)-4-{1-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(121) (*R,S*)-4-{4-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-piperazinyl}-1-piperidineacetic acid,

(122) methyl 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-(*S*)-pyrrolidine-2-carboxylate,

(123) methyl 1-{1-[3-chloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-(S)-pyrrolidine-2-carboxylate,

(124) methyl 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-(*R*)-pyrrolidine-2-carboxylate,

(125) methyl 1-{1-[3-chloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-(*R*)-pyrrolidine-2-carboxylate,

(126) 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-(S)-pyrrolidine-2-carboxylic acid,

(127) 1-{1-[3-chloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-(*S*)-pyrrolidine-2-carboxylic acid,

(128) ethyl 4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethyl-4-hydroxyphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(129) ethyl 4-{1-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(130) ethyl 4-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylate,

(131) ethyl 4-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(132) ethyl 4-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylate,

(133) ethyl 4-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-

oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylate,

(134) 4-{1-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylic acid,

(135) 4-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylic acid,

(136) 4-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylic acid,

(137) 4-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylic acid,

(138) ethyl 4-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylate,

(139) 4-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxo-quinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylic acid,

(140) ethyl 4-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylate,

(141) ethyl 4-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylate,

(142) ethyl 4-{1-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(143) 4-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylic acid,

(144) 4-{1-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylic acid,

(145) 4-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylic acid,

(146) 4-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylic acid,

(147) ethyl 4-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethyl-4-hydroxyphenyl)methyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylate,

(148) ethyl 4-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethyl-4-hydroxyphenyl)methyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylate,

(149) 4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethyl-4-hydroxyphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylic acid,

(150) ethyl 4-{1-[2-[(4-bromo-3,5-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-

2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(151) ethyl 1-{1-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylate,

(152) ethyl 1-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylate,

(153) ethyl 1-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethyl-4-hydroxyphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylate,

(154) ethyl 1-{1-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylate,

(155) ethyl 1-{1-[2-[(4-bromo-3,5-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylate,

(156) 1-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylic acid,

(157) 1-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethyl-4-hydroxyphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylic acid,

(158) 1-{1-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylic acid,

(159) 1-{1-[2-[(4-bromo-3,5-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylic acid,

(160) 1-{1-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylic acid,

(161) ethyl 4-{1-[3,4-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-phenylalanyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(162) 4-{1-[2-[(4-bromo-3,5-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylic acid,

(163) methyl 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-phenylalanyl]-[1,4']bipiperidinyl-4-acetate,

(164) 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-phenylalanyl]-[1,4']bipiperidinyl-4-acetic acid,

(165) ethyl 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(166) ethyl 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylate

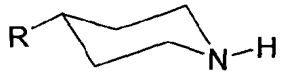
and the salts thereof.

The compounds of general formula I are prepared by methods known in

principle. The following methods have proved particularly suitable for preparing the compounds of general formula I according to the invention:

In order to prepare compounds of general formula (I) wherein Y denotes the NH group and neither X^1 nor X^3 nor X^4 nor R^1 contains a free carboxylic acid function, but otherwise all groups are as hereinbefore defined:

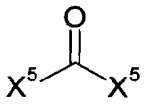
reacting piperidines of general formula



, (IV)

wherein

R is as hereinbefore defined, with carbonic acid derivatives of general formula

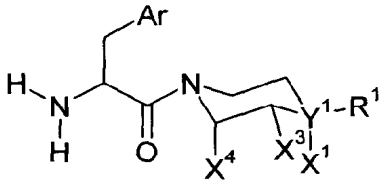


, (V)

wherein

X^5 denotes a nucleofugic group, preferably the 1*H*-imidazol-1-yl, 1*H*-1,2,4-triazol-1-yl, trichloromethoxy or the 2,5-dioxopyrrolidin-1-yloxy group,

and with primary amines of general formula



, (VI)

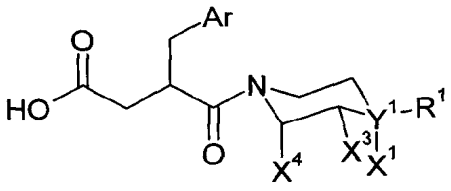
wherein

neither X^1 nor X^3 nor X^4 nor R^1 contains a free carboxylic acid function, but otherwise all groups are as hereinbefore defined.

The fundamentally two-step reactions are normally carried out as one-pot processes, in which, preferably, in the first step, one of the two components (IV) or (VI) is reacted with equimolar amounts of the carbonic acid derivative of general formula (V) in a suitable solvent at lower temperature, then at least equimolar amounts of the other component (IV) or (VI) are added and the reaction is completed at a higher temperature. The reactions with bis-(trichloromethyl)-carbonate are preferably carried out in the presence of at least 2 equivalents (based on bis-(trichloromethyl)-carbonate) of a tertiary base, for example triethylamine, *N*-ethyldiisopropylamine, pyridine, 1,5-diaza-bicyclo-[4,3,0]-non-5-ene, 1,4-diazabicyclo[2,2,2]octane or 1,8-diazabicyclo-[5,4,0]-undec-7-ene. The solvents used, which should be anhydrous, may be for example tetrahydrofuran, dioxane, dimethylformamide, dimethylacetamide, *N*-methyl-2-pyrrolidone, 1,3-dimethyl-2-imidazolidinone or acetonitrile, while if bis-(trichloromethyl)-carbonate is used as the carbonyl component anhydrous chlorohydrocarbons, for example dichloromethane, 1,2-dichloroethane or trichloroethylene are preferred. The reaction temperatures for the first reaction step are between –30°C and +25°C, preferably –5°C and +10°C, for the second reaction step between +15°C and the boiling temperature of the solvent used, preferably between +20°C and +70°C (cf. also: H. A. Staab and W. Rohr, "Synthesen mit heterocyclischen Amiden (Azoliden)", Neuere Methoden der Präparativen Organischen Chemie, Volume V, p. 53-93, Verlag Chemie, Weinheim/Bergstr., 1967; P. Majer and R.S. Randad, J. Org. Chem. 59, p. 1937-1938 (1994); K. Takeda, Y. Akagi, A. Saiki, T. Sukahara and H. Ogura, Tetrahedron Letters 24 (42), 4569-4572 (1983)).

b) In order to prepare compounds of general formula (I) wherein Y denotes the CH_2 group and neither X^1 nor X^3 nor X^4 nor R^1 contains a free carboxylic acid function, but otherwise all groups are as hereinbefore defined:

Coupling a carboxylic acid of general formula



, (VII)

wherein

neither X^1 nor X^3 nor X^4 nor R^1 contains a free carboxylic acid function, but otherwise all groups are as hereinbefore defined,

with a piperidine of general formula

, (IV)

wherein

R has the meanings given hereinbefore.

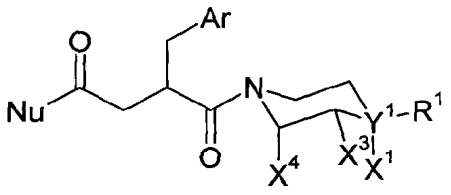
The coupling is preferably carried out using methods known from peptide chemistry (cf. e.g. Houben-Weyl, Methoden der Organischen Chemie, Vol. 15/2), for example using carbodiimides such as e.g. dicyclohexylcarbodiimide (DCC), diisopropyl carbodiimide (DIC) or ethyl-(3-dimethylaminopropyl)-carbodiimide, O-(1H-benzotriazol-1-yl)- N,N-N',N'-tetramethyluronium hexafluorophosphate (HBTU) or tetrafluoroborate (TBTU) or 1H-benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexa-fluorophosphate (BOP). By adding 1-hydroxybenzotriazole (HOBt) or 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HOObt) the reaction speed can be increased. The couplings are normally carried out with equimolar amounts of the coupling components as well as the coupling reagent in solvents such as dichloromethane, tetrahydrofuran, acetonitrile, dimethyl formamide (DMF), dimethyl acetamide (DMA), N-methylpyrrolidone (NMP) or mixtures thereof and at temperatures between -30 and +30°C, preferably -20

and +25°C. If necessary, N-ethyl-diisopropylamine (DIEA) (Hünig base) is preferably used as an additional auxiliary base.

The so-called anhydride process is used as a further coupling method for synthesising compounds of general formula (I) (cf. also: M. Bodanszky, "Peptide Chemistry", Springer-Verlag 1988, p. 58-59; M. Bodanszky, "Principles of Peptide Synthesis", Springer-Verlag 1984, p. 21-27). The Vaughan variant of the mixed anhydride process is preferred (J.R. Vaughan Jr., J. Amer. Chem.Soc. 73, 3547 (1951)), in which the mixed anhydride of the carboxylic acid of general formula (VII) which is to be coupled and monoisobutyl carbonate is obtained, using isobutyl chlorocarbonate in the presence of bases such as 4-methyl-morpholine or 4-ethylmorpholine. The preparation of this mixed anhydride and the coupling with amines are carried out in a one-pot process, using the above-mentioned solvents and at temperatures between -20 and +25°C, preferably 0°C and +25°C.

c) In order to prepare compounds of general formula (I) wherein Y denotes the CH_2 group and neither X^1 nor X^3 nor X^4 nor R^1 contains a free carboxylic acid function, but otherwise all groups are as hereinbefore defined:

Coupling a compound of general formula



, (VIII)

wherein

neither X^1 nor X^3 nor X^4 nor R^1 contains a free carboxylic acid function, but otherwise all groups are as hereinbefore defined, and Nu denotes a leaving group, for example a halogen atom, such as the chlorine, bromine or iodine atom, a C_{1-10}-alkylsulphonyloxy group, a phenylsulphonyloxy or

naphthylsulphonyloxy group optionally mono-, di- or trisubstituted by chlorine or bromine atoms, by methyl or nitro groups, while the substituents may be identical or different, a 1*H*-imidazol-1-yl, a 1*H*-pyrazol-1-yl optionally substituted in the carbon skeleton by 1 or 2 methyl groups, a 1*H*-1,2,4-triazol-1-yl, 1*H*-1,2,3-triazol-1-yl, 1*H*-1,2,3,4-tetrazol-1-yl, a vinyl, propargyl, *p*-nitrophenyl, 2,4-dinitrophenyl, trichlorophenyl, pentachlorophenyl, pentafluorophenyl, pyranyl or pyridinyl, a dimethylaminyloxy, 2(1*H*)-oxopyridin-1-yl-oxy, 2,5-dioxopyrrolidin-1-yloxy, phthalimidyloxy, 1*H*-benzotriazol-1-yloxy or azide group,

with a piperidine of general formula

, (IV)

wherein

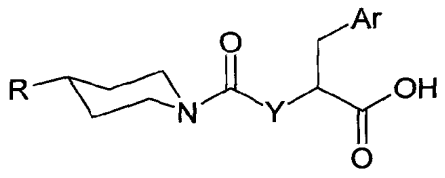
R is as hereinbefore defined.

The reaction is carried out under Schotten-Baumann or Einhorn conditions, i.e. the components are reacted in the presence of at least one equivalent of an auxiliary base at temperatures between -50°C and +120°C, preferably -10°C and +30°C, and optionally in the presence of solvents. The auxiliary bases used are preferably alkali metal and alkaline earth metal hydroxides, e.g. sodium hydroxide, potassium hydroxide or barium hydroxide, alkali metal carbonates, e.g. sodium carbonate, potassium carbonate or caesium carbonate, alkali metal acetates, e.g. sodium or potassium acetate, as well as tertiary amines, e.g. pyridine, 2,4,6-trimethylpyridine, quinoline, triethylamine, N-ethyl-diisopropylamine, N-ethyl-dicyclohexylamine, 1,4-diazabicyclo[2,2,2]octane or 1,8-diazabicyclo[5,4,0]undec-7-ene, the solvents used may be, for example, dichloromethane, tetrahydrofuran, 1,4-dioxane, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methyl-pyrrolidone or mixtures thereof; if alkali metal or alkaline earth metal

hydroxides, alkali metal carbonates or acetates are used as the auxiliary bases, water may also be added to the reaction mixture as cosolvent.

d) In order to prepare compounds of general formula (I) wherein neither X^1 nor X^3 nor X^4 nor R^1 contains a free carboxylic acid function, but otherwise all groups are as hereinbefore defined:

Coupling a carboxylic acid of general formula

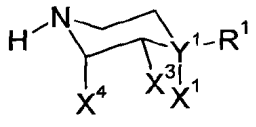


, (IX)

wherein

Ar, R and Y are as hereinbefore defined,

with a cyclic secondary amine of general formula



, (X)

wherein
neither X^1 nor X^3 nor X^4 nor R^1 contains a free carboxylic acid function, but otherwise the groups are as hereinbefore defined.

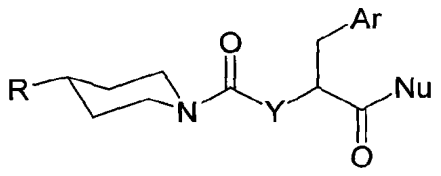
The coupling is preferably carried out using methods known from peptide chemistry (cf. e.g. Houben-Weyl, Methoden der Organischen Chemie, Vol. 15/2), for example using carbodiimides such as e.g. dicyclohexylcarbodiimide (DCC), diisopropyl carbodiimide (DIC) or ethyl-(3-dimethylaminopropyl)-carbodiimide, O-(1H-benzotriazol-1-yl)- N,N-N',N'-tetramethyluronium

hexafluorophosphate (HBTU) or tetrafluoroborate (TBTU) or 1H-benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP). By adding 1-hydroxybenzotriazole (HOBt) or 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HOObt) the reaction speed can be increased. The couplings are normally carried out with equimolar amounts of the coupling components as well as the coupling reagent in solvents such as dichloromethane, tetrahydrofuran, acetonitrile, dimethyl formamide (DMF), dimethyl acetamide (DMA), N-methylpyrrolidone (NMP) or mixtures thereof and at temperatures between -30 and +30°C, preferably -20 and +25°C. If necessary, N-ethyl-diisopropylamine (DIEA) (Hünig base) is preferably used as an additional auxiliary base.

The so-called anhydride process is used as a further coupling method for synthesising compounds of general formula (I) (cf. also: M. Bodanszky, "Peptide Chemistry", Springer-Verlag 1988, p. 58-59; M. Bodanszky, "Principles of Peptide Synthesis", Springer-Verlag 1984, p. 21-27). The Vaughan variant of the mixed anhydride process is preferred (J.R. Vaughan Jr., J. Amer. Chem.Soc. 73, 3547 (1951)), in which the mixed anhydride of the carboxylic acid of general formula (IX) which is to be coupled and monoisobutyl carbonate is obtained, using isobutyl chlorocarbonate in the presence of bases such as 4-methyl-morpholine or 4-ethylmorpholine. The preparation of this mixed anhydride and the coupling with amines of general formula (X) are carried out in a one-pot process, using the above-mentioned solvents and at temperatures between -20 and +25°C, preferably 0°C and +25°C.

e) In order to prepare compounds of general formula (I) wherein neither X^1 nor X^3 nor X^4 nor R^1 contains a free carboxylic acid function, but otherwise all groups are as hereinbefore defined:

Coupling a compound of general formula

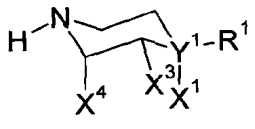


, (XI)

wherein

Ar, R and Y are as hereinbefore defined and Nu denotes a leaving group, for example a halogen atom, such as the chlorine, bromine or iodine atom, a C_{1-10}-alkylsulphonyloxy group, a phenylsulphonyloxy or naphthylsulphonyloxy group optionally mono-, di- or trisubstituted by chlorine or bromine atoms, by methyl or nitro groups, while the substituents may be identical or different, a 1*H*-imidazol-1-yl, a 1*H*-pyrazol-1-yl optionally substituted in the carbon skeleton by 1 or 2 methyl groups, a 1*H*-1,2,4-triazol-1-yl, 1*H*-1,2,3-triazol-1-yl, 1*H*-1,2,3,4-tetrazol-1-yl, a vinyl, propargyl, *p*-nitrophenyl, 2,4-dinitrophenyl, trichlorophenyl, pentachlorophenyl, pentafluorophenyl, pyranyl or pyridinyl, a dimethylaminyloxy, 2(1*H*)-oxopyridin-1-yl-oxy, 2,5-dioxopyrrolidin-1-yloxy, phthalimidyloxy, 1*H*-benzotriazol-1-yloxy or azide group,

with a cyclic secondary amine of general formula



, (X)

wherein

neither X^1 nor X^3 nor X^4 nor R^1 contains a free carboxylic acid function, but otherwise the groups are as hereinbefore defined.

The reaction is carried out under Schotten-Baumann or Einhorn conditions, i.e. the components are reacted in the presence of at least one equivalent of

an auxiliary base at temperatures between -50°C and +120°C, preferably -10°C and +30°C, and optionally in the presence of solvents. The auxiliary bases used are preferably alkali metal and alkaline earth metal hydroxides, e.g. sodium hydroxide, potassium hydroxide or barium hydroxide, alkali metal carbonates, e.g. sodium carbonate, potassium carbonate or caesium carbonate, alkali metal acetates, e.g. sodium or potassium acetate, as well as tertiary amines, e.g. pyridine, 2,4,6-trimethylpyridine, quinoline, triethylamine, N-ethyl-diisopropylamine, N-ethyl-dicyclohexylamine, 1,4-diazabicyclo[2,2,2]octane or 1,8-diazabicyclo[5,4,0]undec-7-ene, the solvents used may be, for example, dichloromethane, tetrahydrofuran, 1,4-dioxane, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methyl-pyrrolidone or mixtures thereof; if alkali metal or alkaline earth metal hydroxides, alkali metal carbonates or acetates are used as the auxiliary bases, water may also be added to the reaction mixture as cosolvent.

f) In order to prepare compounds of general formula (I) wherein X^1, X^3, X^4 or R^1 contains a free carboxylic acid function, but otherwise all the groups are as hereinbefore defined:

hydrolysis of carboxylic acid esters of general formula (I), wherein either X^1 or X^3 or X^4 or R^1 contains a carboxylic acid ester function and all the other groups are as hereinbefore defined. The hydrolysis may be carried out with acid or alkaline catalysis under the conditions familiar to those skilled in the art. Acid-catalysed hydrolysis takes place in the presence of strong organic or inorganic acids, for example methanesulphonic acid, *p*-toluenesulphonic acid, hydrochloric acid, hydrobromic acid or sulphuric acid, preferably in the presence of water-miscible solvents, for example methanol, ethanol or 1,4-dioxane, and at temperatures between 0°C and the boiling temperature of the hydrolysis mixture. It is advantageous to carry out alkaline saponification of the carboxylic acid esters of general formula (I), optionally also in the presence of water-miscible cosolvents. To do this, at least 1 equivalent, based on the particular carboxylic acid ester, of an inorganic base such as aqueous lithium hydroxide solution, sodium, potassium or barium hydroxide solution is used. Suitable temperatures are between 0°C and 50°C, room temperature

being preferred. The desired acid can be released from the salt initially obtained by acidification in known manner.

The new carboxylic acids and carboxylic acid esters of general formula (I) according to the invention contain one or more chiral centres. If for example there are two chiral centres the compounds may occur in the form of two pairs of diastereomeric antipodes. The invention covers the individual isomers as well as the mixtures thereof.

The diastereomers may be separated on the basis of their different physico-chemical properties, e.g. by fractional crystallisation from suitable solvents, by high pressure liquid or column chromatography, using chiral or preferably non-chiral stationary phases.

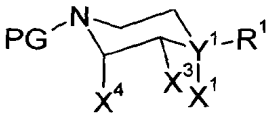
Racemates covered by general formula (I) may be separated for example by HPLC on suitable chiral stationary phases (e.g. Chiral AGP, Chiralpak AD). Racemates which contain a basic or acidic function can also be separated via the diastereomeric, optically active salts which are produced on reacting with an optically active acid, for example (+) or (-)-tartaric acid, (+) or (-)-diacetyl tartaric acid, (+) or (-)-monomethyl tartrate or (+)-camphorsulphonic acid, or an optically active base, for example with (R)-(+)-1-phenylethylamine, (S)-(-)-1-phenylethylamine or (S)-brucine.

According to a conventional method of separating isomers, the racemate of a compound of general formula (I) is reacted with one of the above-mentioned optically active acids or bases in equimolar amounts in a solvent and the resulting crystalline, diastereomeric, optically active salts thereof are separated using their different solubilities. This reaction may be carried out in any type of solvent provided that it is shows a sufficient difference in terms of the solubility of the salts. Preferably, methanol, ethanol or mixtures thereof, for example in a ratio by volume of 50:50, are used. Then each of the optically active salts is dissolved in water, carefully neutralised with a base such as sodium carbonate or potassium carbonate, or with a suitable acid, e.g. dilute

hydrochloric acid or aqueous methanesulphonic acid, and in this way the corresponding free compound is obtained in the (+) or (-) form.

The (R) or (S) enantiomer alone or a mixture of two optically active diastereomeric compounds covered by general formula I may also be obtained by performing the syntheses described above with a suitable reaction component in the (R) or (S) configuration.

The starting compounds of general formula (IV) may be obtained, if they are not known from the literature or even commercially available, according to the processes described in WO 98/11128 and DE 199 52 146. The starting compounds of general formula (V) are commercially available. Compounds of general formula (VI) may be obtained by methods familiar to the peptide chemist from protected phenylalanines and amines of general formula (X). The starting compounds of general formula (VII) are obtained for example by reacting cyclic secondary amines of general formula (X) with 2-(alkoxycarbonylmethyl)-3-aryl-propanoic acids and subsequently hydrolytically cleaving the alkyl group. The 2-(alkoxycarbonylmethyl)-3-aryl-propanoic acids required may be prepared analogously to methods known from the literature (Saul G. Cohen and Aleksander Milovanovic, J. Am. Chem. Soc. 90, 3495-3502 [1968]; Hiroyuki Kawano, Youichi Ishii, Takao Ikariya, Masahiko Saburi, Sadao Yoshikawa, Yasuzo Uchida and Hidenori Kumobayashi, Tetrahedron Letters 28, 1905-8 [1987]). Carboxylic acids of general formula IX have been described in WO 98/11128 or may be prepared using the methods described therein from generally available starting materials. The cyclic secondary amines of general formula (X) may be synthesised from compounds of general formula



, (XII)

wherein PG denotes a cleavable protective group, for example by

hydrogenolysis of a phenylmethyl group. The preliminary products for synthesising the compounds of general formula (XII) are obtainable from starting materials which are commercially available or easily obtained by common methods. Finally, the starting compounds of general formulae VIII and XI may be prepared from the corresponding carboxylic acids (VII) or (IX) using known standard methods.

The compounds of general formula I obtained may, if they contain suitable basic functions, be converted, particularly for pharmaceutical use, into their physiologically acceptable salts with inorganic or organic acids. Suitable acids include for example hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid, *p*-toluenesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, mandelic acid, malic acid, citric acid, tartaric acid or maleic acid.

Moreover, the new compounds of formula (I), if they contain a carboxylic acid function, may if desired be converted into the addition salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable addition salts thereof. Suitable bases for this include, for example, sodium hydroxide, potassium hydroxide, ammonia, cyclohexylamine, dicyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The new compounds of general formula I and the physiologically acceptable salts thereof have CGRP-antagonistic properties and exhibit good affinities in CGRP receptor binding studies. The compounds display CGRP-antagonistic properties in the pharmacological test systems described hereinafter.

The following experiments were carried out to demonstrate the affinity of the compounds of general formula I for human CGRP-receptors and their antagonistic properties:

A. Binding studies with SK-N-MC cells (expressing the human CGRP receptor)

SK-N-MC cells are cultivated in "Dulbecco's modified Eagle medium". The medium is removed from confluent cultures. The cells are washed twice with PBS buffer (Gibco 041-04190 M), detached by the addition of PBS buffer mixed with 0.02% EDTA, and isolated by centrifuging. After resuspension in 20 ml of "Balanced Salts Solution" [BSS (in mM): NaCl 120, KCl 5.4, $NaHCO_3$ 16.2, $MgSO_4$ 0.8, $NaHPO_4$ 1.0, $CaCl_2$ 1.8, D-glucose 5.5, HEPES 30, pH 7.40] the cells are centrifuged twice at 100 x g and resuspended in BSS. After the number of cells has been determined, the cells are homogenised using an Ultra-Turrax and centrifuged for 10 minutes at 3000 x g. The supernatant is discarded and the pellet is recentrifuged in Tris buffer (10 mM Tris, 50 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.40 enriched with 1% bovine serum albumin and 0.1% bacitracin), and resuspended (1 ml / 1000000 cells). The homogenised product is frozen at -80°C. The membrane preparations are stable for more than 6 weeks under these conditions.

After thawing, the homogenised product is diluted 1:10 with assay buffer (50 mM Tris, 150 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.40) and homogenised for 30 seconds with an Ultra-Turrax. 230 µl of the homogenised product are incubated for 180 minutes at ambient temperature with 50 pM ^{125}I-iodotyrosyl-Calcitonin-Gene-Related Peptide (Amersham) and increasing concentrations of the test substances in a total volume of 250 µl. The incubation is ended by rapid filtration through GF/B-glass fibre filters treated with polyethyleneimine (0.1%) using a cell harvester. The protein-bound radioactivity is measured using a gamma counter. Non-specific binding is defined as the bound radioactivity in the presence of 1 µM human CGRP-alpha during incubation.

The concentration binding curves are analysed using computer-aided non-linear curve matching.

The compounds of general formula (I) show IC_{50} values $\leq$ 10000 nM in the test described.

B. CGRP Antagonism in SK-N-MC cells

SK-N-MC cells (1 million cells) are washed twice with 250 µl incubation buffer (Hanks' HEPES, 1 mM 3-isobutyl-1-methylxanthine, 1% BSA, pH 7.4) and pre-incubated at 37°C for 15 minutes. After the addition of CGRP (10 µl) as agonist in increasing concentrations (10^{-11} to 10^{-6} M), or additionally the substance in 3 to 4 different concentrations, the mixture is incubated for another 15 minutes.

Intracellular cAMP is then extracted by the addition of 20 µl of 1M HCl and centrifugation (2000 x g, 4°C, for 15 minutes). The supernatants are frozen in liquid nitrogen and stored at -20°C.

The cAMP contents of the samples are determined by radioimmunoassay (Messrs. Amersham) and the pA_2 values of antagonistically acting substances are determined graphically.

The compounds of general formula (I) exhibit CGRP-antagonistic properties in the *in vitro* test model described, in a dosage range between 10^{-11} and 10^{-5} M.

In view of their pharmacological properties the compounds of general formula I and the salts thereof with physiologically acceptable acids are thus suitable for the acute and prophylactic treatment of headaches, particularly migraine or cluster headaches. Moreover, the compounds of general formula I also have a positive effect on the following diseases: "complex regional pain syndrome", non-insulin-dependent diabetes mellitus ("NIDDM"), cardiovascular diseases, morphine tolerance, diarrhoea caused by clostridium toxin, skin diseases, particularly thermal and radiation-induced skin damage including sunburn, inflammatory diseases, e.g. inflammatory diseases of the joints (arthritis), inflammatory lung diseases, allergic rhinitis, asthma, diseases accompanied

by excessive vasodilatation and resultant reduced blood supply to the tissues, e.g. shock and sepsis. The symptoms of menopausal hot flushes caused by vasodilatation and increased blood flow in oestrogen-deficient women are favourably affected by the CGRP-antagonists of the present application in a preventive and acute-therapeutic capacity, this therapeutic approach being distinguished from hormone replacement by the absence of side effects. In addition, the compounds according to the invention have a general pain-relieving effect.

The dosage required to achieve a corresponding effect is conveniently 0.001 to 30 mg/kg of body weight, preferably 0.01 to 5 mg/kg of body weight, when administered intravenously or subcutaneously, and 0.01 to 50 mg/kg of body weight, preferably 0.1 to 30 mg/kg of body weight when administered orally, nasally or by inhalation, 1 to 3 x a day in each case.

For this purpose, the compounds of general formula I prepared according to the invention may be formulated with other active substances such as e.g. antiemetics, prokinetics, neuroleptics, antidepressants, neurokinine antagonists, anticonvulsants, histamine-H1 receptor antagonists, antimuscarinics, β-blockers, α-agonists and α-antagonists, ergot alkaloids, mild analgesics, non-steroidal antiinflammatories, corticosteroids, calcium antagonists, 5-HT_{1D} agonists or other anti-migraine agents, together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinyl pyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, metered dose aerosols or suppositories.

Thus other active substances which may be used for the combinations mentioned above include for example meloxicam, ergotamine,

dihydroergotamine, metoclopramide, domperidone, diphenhydramine, cyclizine, promethazine, chlorpromazine, dexamethasone, flunarizine, dextropropoxyphene, meperidine, propranolol, nadolol, atenolol, clonidine, indoramin, carbamazepine, phenytoin, valproate, amitryptilin, lidocaine, diltiazem or sumatriptan and other 5-HT_{1D} agonists such as e.g. naratriptan, zolmitriptan, avitriptan, rizatriptan and eletriptan. The dosage for these active substances is expediently 1/5 of the lowest usually recommended dose to 1/1 of the normally recommended dose, i.e. for example 20 to 100 mg of sumatriptan.

The invention further relates to the use of the compounds of general formula (I) as valuable adjuvants for the production and purification (by affinity chromatography) of antibodies as well as in RIA and ELISA assays, after suitable radioactive labelling, for example by direct labelling with ^{125}I or ^{131}I or by tritiation of suitable precursors, for example by replacing halogen atoms with tritium, and as a diagnostic or analytical aid in neurotransmitter research.

The Examples that follow are intended to illustrate the invention more fully:

Preliminary remarks:
The compounds were prepared in some cases by conventional methods of synthesis and in other cases using methods of combined chemistry.

The automatic synthesiser used was the ASW2000 machine made by Chemspeed Ltd., Rheinstraße 32, CH-4302 Augst, Switzerland.

As a rule, IR, ^1H-NMR and/or mass spectra have been obtained for all the compounds prepared by conventional methods. Unless otherwise stated, R_f values were obtained using ready-made silica gel TLC plates 60 F254 (E. Merck, Darmstadt, Item no. 1.05714) without chamber saturation. If no detailed information is given as to the configuration, it is not clear whether it is a pure enantiomer or whether partial or even complete racemisation has occurred. The following eluants or eluant mixtures were used for the chromatography:

El A = ethyl acetate/methanol 100/5 v/v

El B = ethyl acetate/methanol 9/1 v/v

El C = ethyl acetate/methanol/conc. ammonia 80/20/1 v/v/v

El D = dichloromethane/cyclohexane/methanol/conc.ammonia 70/15/15/2 v/v/v/v

El E = ethyl acetate/glacial acetic acid 99/1 v/v

El F = ethyl acetate/methanol/glacial acetic acid 90/10/1 v/v/v

El G = dichloromethane/methanol/conc. ammonia 90/9/1 v/v/v

El H = petroleum ether/ethyl acetate 4/6 v/v

El I = dichloromethane/methanol/glacial acetic acid 90/10/2.5 v/v/v

El K = dichloromethane/isopropanol 9/1 v/v

El M = dichloromethane/methanol/conc. ammonia 75/25/5 v/v/v

El N = dichloromethane/ethyl acetate 1/1 v/v

El O = dichloromethane/methanol 9/1 v/v

El P = dichloromethane/ethyl acetate/cyclohexane/methanol/conc. ammonia 60/16/5/5/0.6 v/v/v/v/v

El Q = dichloromethane/methanol/conc. ammonia 80/20/2 v/v/v

El R = dichloromethane/methanol/glacial acetic acid 80/20/1 v/v/v

El S = dichloromethane/methanol 9/1 v/v (Alox TLC plates [E. Merck, Darmstadt])

El T = dichloromethane/methanol/glacial acetic acid 70/30/3 v/v/v

El U = ethyl acetate/petroleum ether 2/1 v/v

El V = ethyl acetate/petroleum ether 1/4 v/v

El W = ethyl acetate/petroleum ether 3/7 v/v

El X = petroleum ether/ethyl acetate/glacial acetic acid 8/2/0.5 v/v/v

El Y = ethyl acetate/petroleum ether 1/9 v/v

El Z = toluene/petroleum ether/ethyl acetate 5/5/2 v/v/v

El AA = ethyl acetate/petroleum ether/triethylamine 5/5/0.1 v/v/v

El BB = dichloromethane/methanol 3/1 v/v (Alox TLC plates [E. Merck, Darmstadt])

El DD = ethyl acetate/methanol/conc. ammonia 70/30/3 v/v/v

El EE = dichloromethane/ethanol 9/1 v/v

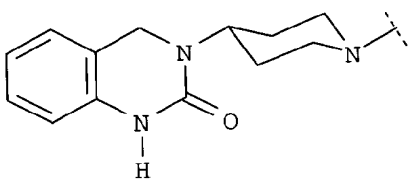
El FF = dichloromethane/ethanol 50/1 v/v

El GG =	dichloromethane/ethanol 40/1 v/v
El HH =	dichloromethane/methanol 5/1 v/v
El II =	ethyl acetate/methanol/conc. ammonia 90/10/1 v/v/v
El KK =	ethyl acetate/methanol/conc. ammonia 60/40/4 v/v/v
El LL =	ethyl acetate/methanol/conc. ammonia 50/50/5 v/v/v
El MM =	ethyl acetate/cyclohexane 1/1 v/v
El NN =	ethyl acetate/cyclohexane 2/8 v/v
El OO =	dichloromethane/methanol/conc. ammonia 70/30/3 v/v/v

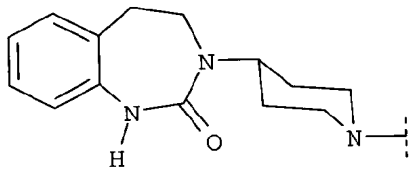
The following abbreviations are used in the description of the test:

mp.:	melting point
(Z):	(decomposition)
DIEA:	*N*,*N*-diisopropylethylamine
Boc:	(1,1-dimethylethoxy)carbonyl
TBTU:	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
HOBt:	1-hydroxybenzotriazole-hydrate
CDT:	1,1'-carbonyldi-(1,2,4-triazole)
PyBroP:	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
HATU:	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate
THF:	tetrahydrofuran
DMF:	dimethylformamide
EE:	ethyl acetate
PE:	petroleum ether
LM:	solvent
ZT	room temperature
Ser. no:	serial no.

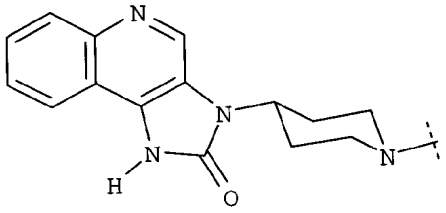
The meanings of the symbols consisting of letters and numbers used in the Examples are shown in the following summary:



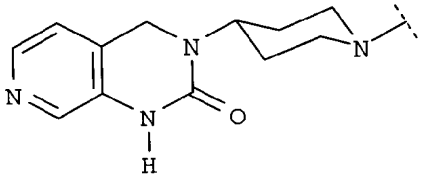
N1



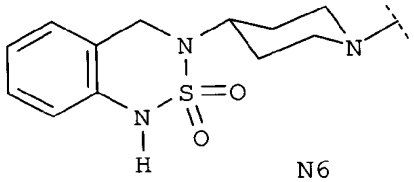
N2



N4



N5



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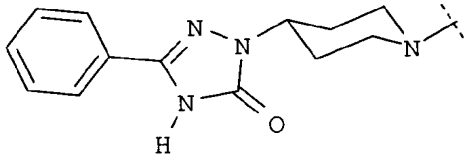

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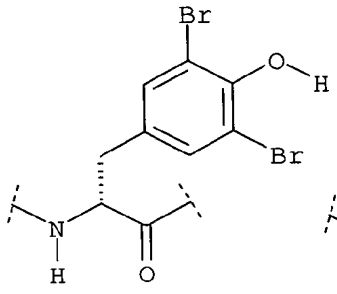

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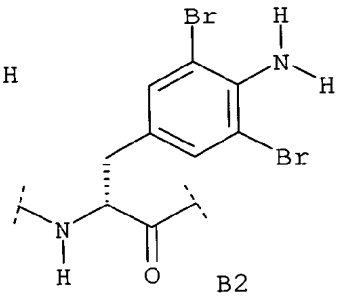

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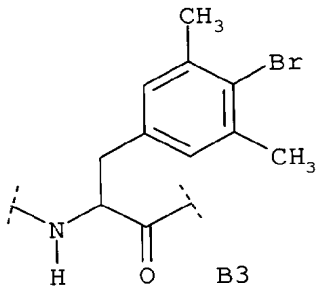

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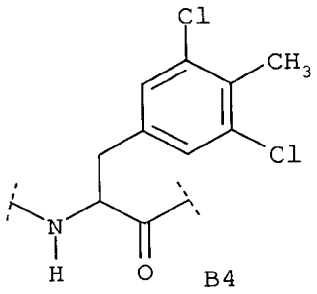

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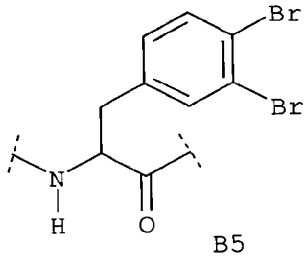

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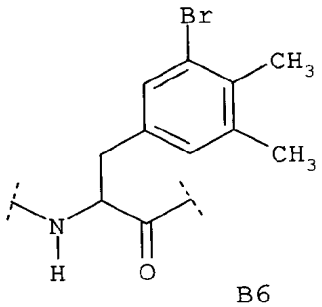

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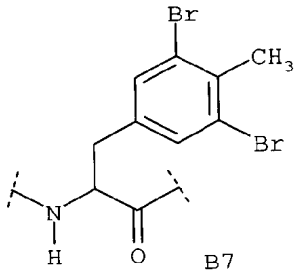
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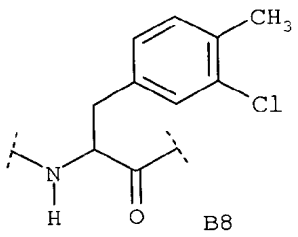
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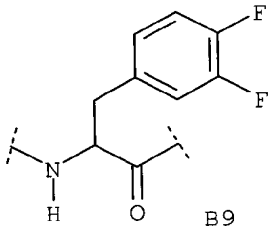
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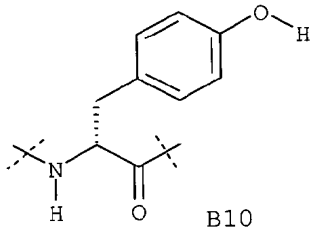
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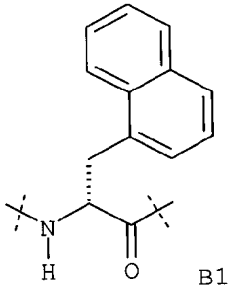
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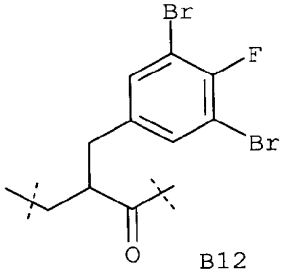
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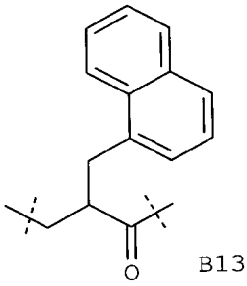
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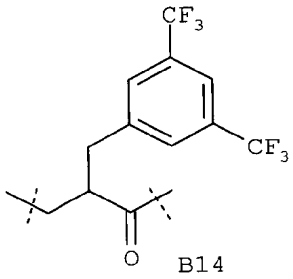
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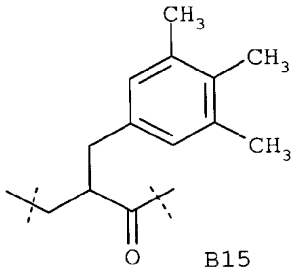
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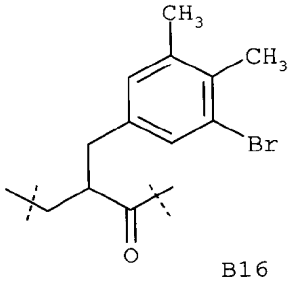
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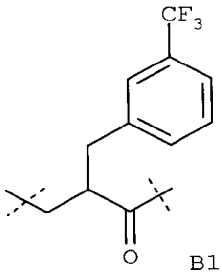
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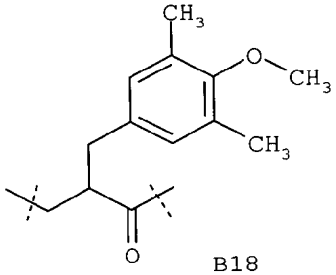
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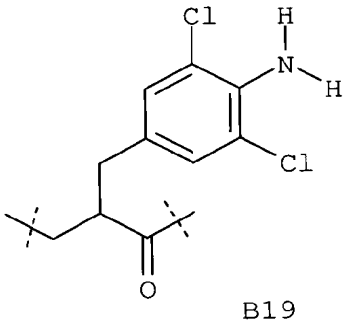

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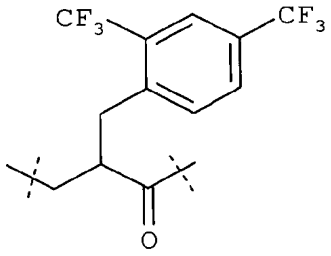

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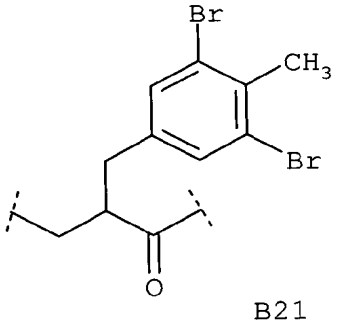

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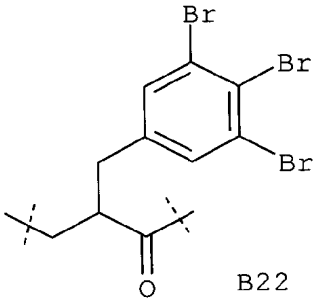

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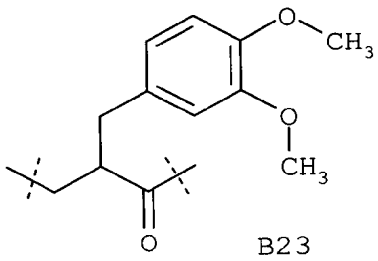

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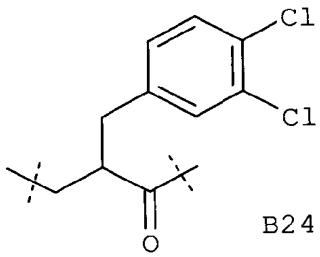

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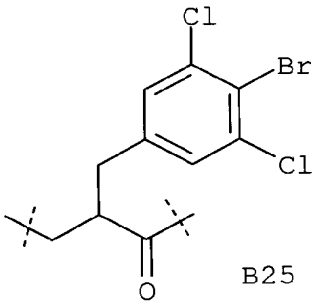

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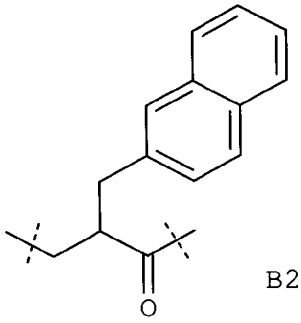

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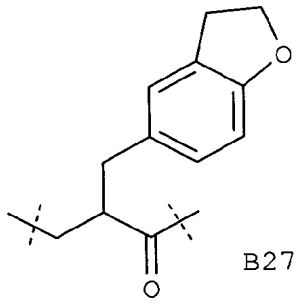

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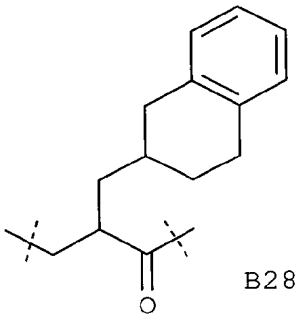

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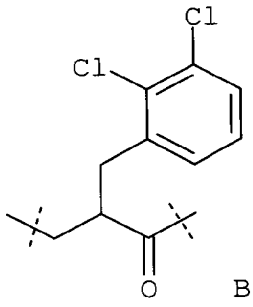

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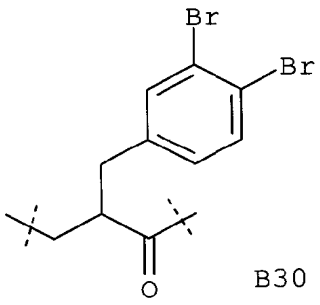

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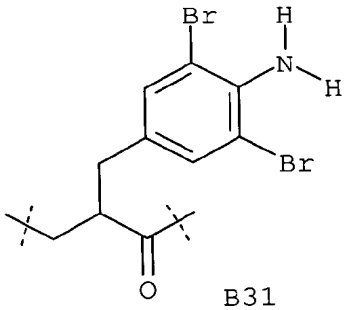

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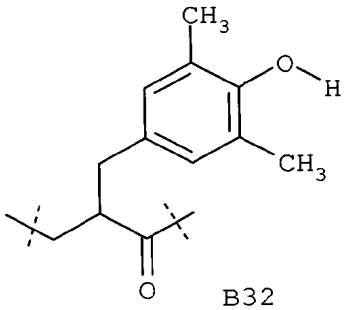

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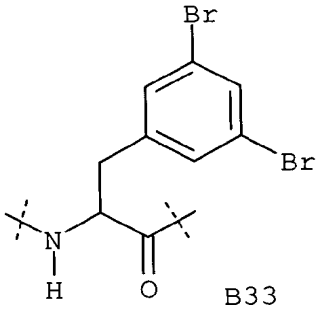

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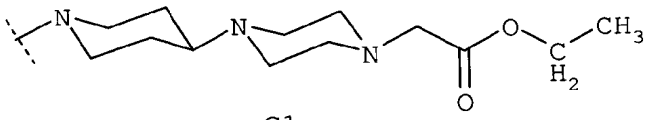

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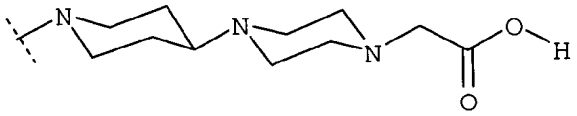

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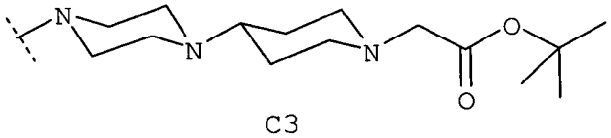

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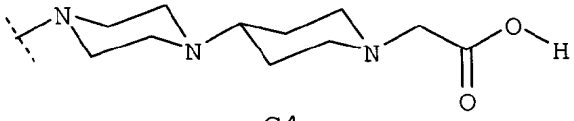

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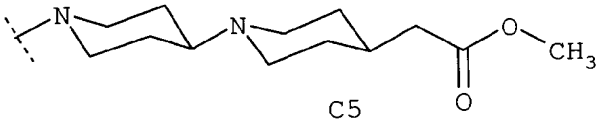

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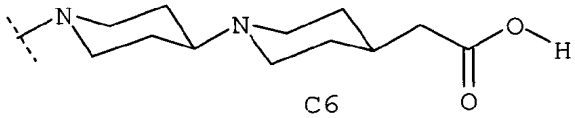

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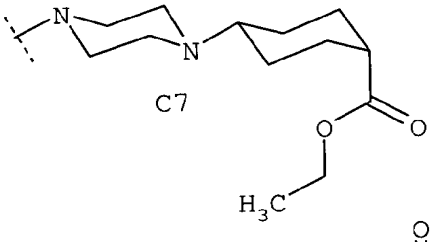

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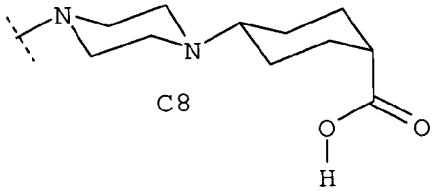

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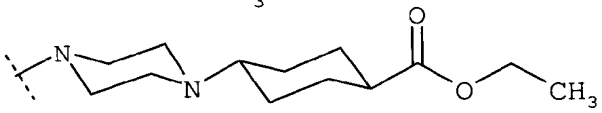

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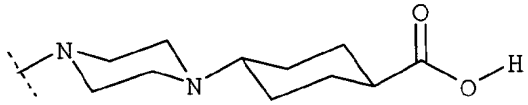

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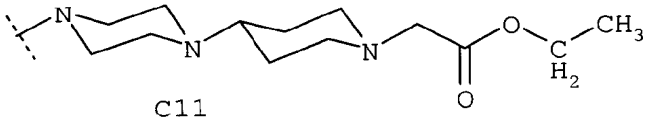

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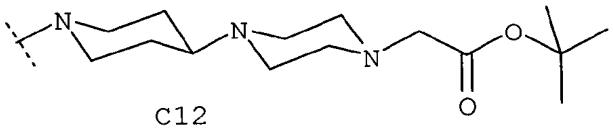

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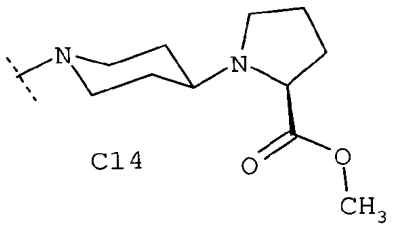
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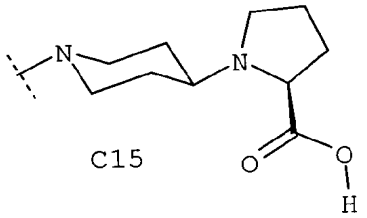
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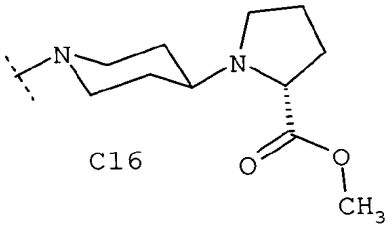
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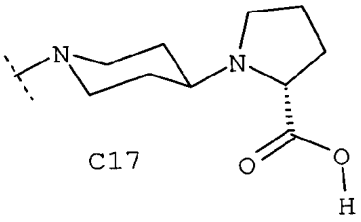
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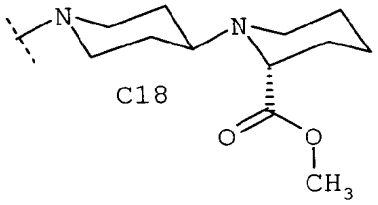
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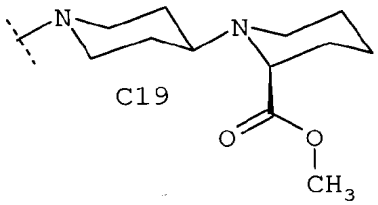
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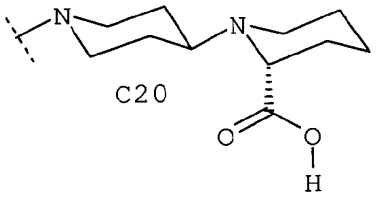
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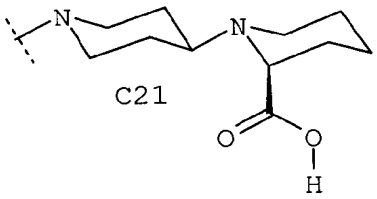
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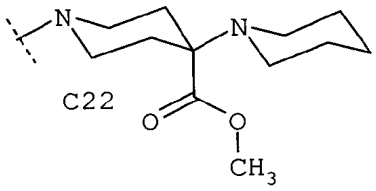
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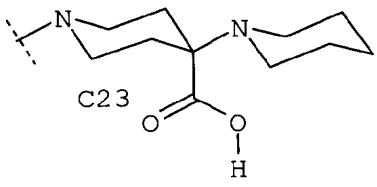
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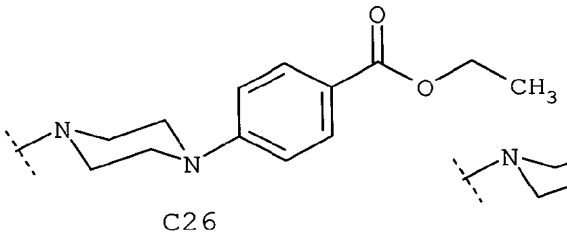
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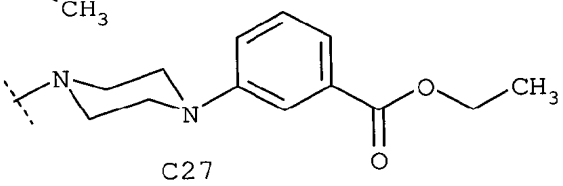
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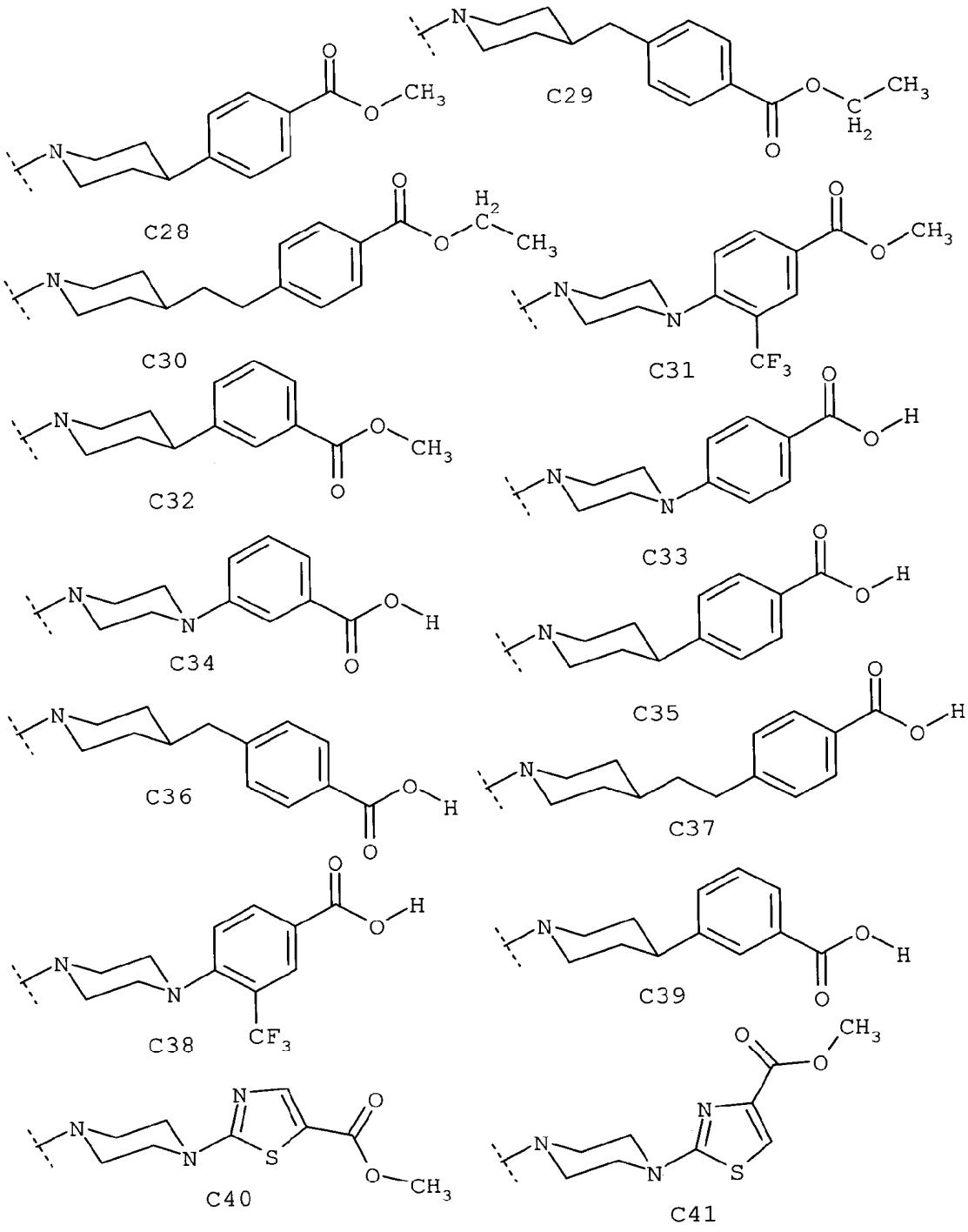
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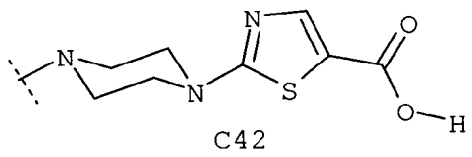

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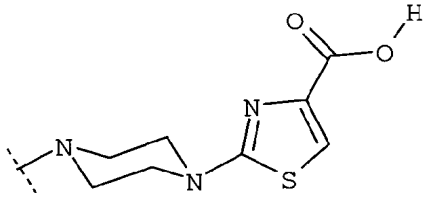

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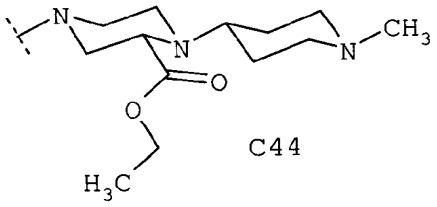

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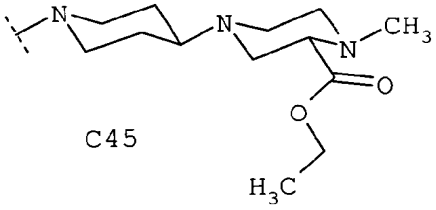

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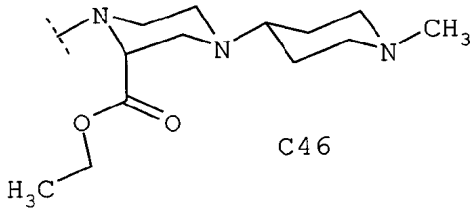

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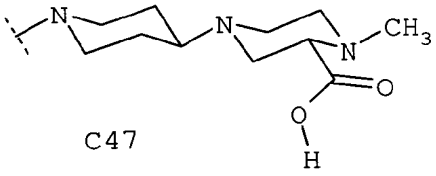

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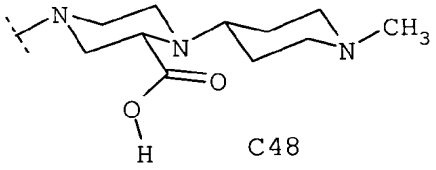

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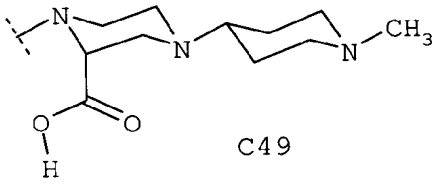

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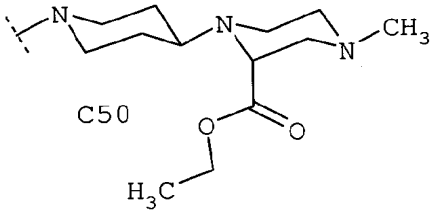

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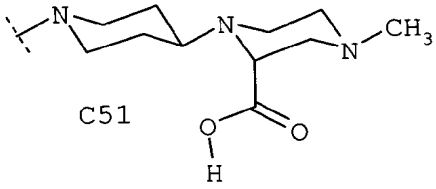

C51

A. Preparation of intermediate compounds

Example A1

(*R,S*)-3,4-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-carbonyl]-phenylalanine

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150 ml 1M sodium hydroxide solution were added to the solution of 20.0 g (0.033 mol) (*R,S*)-3,4-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-phenylalanine ethyl ester in 500 ml of ethanol and the mixture was then stirred for 3.5 hours at room temperature. The solvent was eliminated using the rotary evaporator and the residue was acidified with 1M hydrochloric acid. The precipitated precipitate was suction filtered, washed thoroughly with water and dried at 70°C in the circulating air dryer. 10.0 g (52% of theory) of the desired colourless crystalline substance were obtained, R_f 0.62 (El M).

IR (KBr): 1705, 1645 cm^{-1} (C=O)

The following compounds of general formula N-B-C were prepared analogously:

N	B	C	Remarks	% yield	El	R_f	MS	IR [cm^{-1}]	mp. [°C]
N1	B6	OH	from N1-CO-B6-OEt with aq. 1M NaOH, then aq. 1M HCl	96			ESI: $(M-H)^-$ = 527/529 (Br)	1630, 1701 (C=O)	173-175
N1	B7	OH	from N1-CO-B7-OEt with aq. 1M NaOH, then aq. 1M HCl	62	D	0.19		1705 (C=O)	colour-less crystals
N1	B10	OH	from N1-CO-B10-OMe with aq. 1M NaOH, then aq. 1M HCl	79			ESI: $(M+Na)^+$ = 481		colour-less crystals

N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
N1	B11	OH	from N1-CO-B11-OMe with aq. 1M LiOH, then aq. citric acid	61			ESI: $(M+H)^+$ = 439		colour-less crystals
N1	B3	OH	from N1-CO-B3-OEt with aq. 1M LiOH, then aq. citric acid	95					colour-less crystals
N1	B4	OH	from N1-CO-B4-OEt with aq. 1M NaOH, then aq. 1M HCl	96	B	0.12	ESI: $(M-H)^-$ = 503/505/507 (Cl_2)		colour-less crystals
N1	B12	OH	from N1-CO-B12[α-CO_2Et]-OEt with aq. 40% NaOH, then aq. 5M HCl	100	G	0.11	ESI: $(M-H)^-$ = 594/596/598 (Br_2)		colour-less crystals
N1	B15	OH	from N1-CO-B15[α-CO_2Et]-OEt with aq. 1M NaOH, then aq. 1M HCl	46	F	0.60	ESI: $(M-H)^-$ = 462; $(M+H)^+$ = 464	1647 (C=O)	colour-less crystals
N1	B16	OH	from N1-CO-B16[α-CO_2Et]-OEt with aq. 1M NaOH, then aq. 1M HCl	100	F	0.49	ESI: $(M-H)^-$ = 526	1645 (C=O)	colour-less crystals
N1	B19	OH	from N1-CO-B19[α-CO_2Et]-OEt with aq. 1M NaOH, then aq. 1M HCl	50					colour-less crystals
N1	B20	OH	from N1-CO-B20[α-CO_2Et]-OEt with aq. 1M NaOH, then aq. 1M HCl	55	D	0.23	M^+ = 557; ESI: $(M-H)^-$ = 556		colour-less crystals
N1	B22	OH	from N1-CO-B22[α-CO_2Et]-OEt with aq. 1M NaOH, then aq. 1M HCl	91	D	0.25	ESI: $(M-H)^-$ = 654/656/658/660 (Br_3)	1641 (C=O)	colour-less crystals
N1	B25	OH	from N1-CO-B25[α-CO_2Et]-OEt with aq. 1M KOH, then aq. 1M HCl	62	F	0.4	no M^+, decomposition compatible with structure	1726, 1705, 1641 (C=O)	colour-less crystals

N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
N1	B27	OH	from N1-CO-B27[α-CO_2Et]-OEt with aq. 1M NaOH, then aq. 1M HCl	87	F	0.55			colour-less crystals
N1	B29	OH	from N1-CO-B29[α-CO_2Et]-OEt with KOH, then aq. 10M HCl	100	D	0.46	no M^+, decomposition compatible with structure	1640 (C=O)	colour-less crystals
N1	B21	OH	from N1-CO-B21[α-CO_2Et]-OEt with 1M NaOH, then aq. 1M HCl	71	D	0.16	no M^+, decomposition compatible with structure	1724, 1643 (C=O)	colour-less crystals
N1	B8	OH	from N1-CO-B8-OEt with 1M NaOH, then aq. 1M HCl	90	Q	0.23		1730, 1665 (C=O)	colour-less crystals
N1	B30	OH	from N1-CO-B30[α-CO_2Et]-OEt with 1M NaOH, then aq. 1M HCl	100	F	0.45	ESI: $(M-H)^-$ = 576/578/580 (Br_2)		colour-less crystals
N1	B23	OH	from N1-CO-B23-OMe with 1M NaOH, then aq. 1M HCl	96					
N1	B24	OH	from N1-CO-B24[α-CO_2Et]-OEt with 1M NaOH, then aq. 1M HCl	98	F	0.29			colour-less crystals
N6	B21	OH	from N6-CO-B21[α-CO_2Et]-OEt with 1M NaOH, then aq. 1M HCl	89			ESI: $(M-H)^-$ = 626/628/630 (Br_2)		colour-less crystals
N2	B2	OH	from N2-CO-B2-OMe with 1M LiOH, then aq. 1M HCl	96	M	0.49	ESI: $(M-H)^-$ = 606/608/610 (Br_2)	1724, 1660 (C=O)	colour-less crystals

Example A2

3,4-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D,L-phenylalanine ethyl ester

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9.7 g (0.056 Mol) CDT were added to an ice-cooled suspension of 18.0 g (0.051 Mol) (*R,S*)- 3,4-dibromo-phenylalanine ethyl ester in 300 ml THF. The reaction mixture was then stirred for 1 hour at 0 °C and 1 hour at ambient temperature and then combined with 11.9 g (0.051 mol) 3-(4-piperidinyl)-1,3,4,5-tetrahydro-1,3-benzodiazepin-2-one. The mixture was refluxed for 4 hours and left to stand overnight at ambient temperature. The reaction mixture was concentrated by evaporation using the rotary evaporator, the residue was combined with 300 ml aqueous sodium hydrogen carbonate solution and stirred for 30 minutes. The aqueous solution was decanted off, the residue was combined with 150 ml of ethanol and refluxed. After cooling the white solid obtained was suction filtered, washed with ethanol and dried at 50°C . 20.0 g (64% of theory) of the product were obtained, with an R_f value of 0.68 (El D)

IR (KBr): 1734, 1680, 1662 (C=O) cm^{-1}

The following compounds of general formula N-B-C were prepared analogously:

N	B	C	Remarks	% yield	El	R_f	MS	IR [cm^{-1}]	mp. [°C]
N1	B6	OEt	from N1-H, CDT and H-B6-OEt in THF	90	B	0.67	M^+ = 557	1732, 1662 (C=O)	colourless crystals
N1	B7	OEt	from N1-H, CDT and H-B7-OEt in THF	100	D	0.45			colourless crystals
N1	B11	OMe	from N1-H, CDT, H-B11-OMe * HCl and DIEA in THF	97			ESI: $(M-H)^-$ = 471		

N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
N1	B10	OMe	from N1-H, CDT, H-B10-OMe * HCl and DIEA in THF	63	G	0.55	ESI: $(M+H)^+$ = 453		
N1	B3	OEt	from N1-H, CDT, H-B3-OEt * HCl and NEt_3 in THF/DMF 2/1 v/v	92				1739, 1682, 1664 (C=O)	colourless crystals
N1	B4	OEt	from N1-H, CDT and H-B4-OEt in THF	73	B	0.50	ESI: $(M+H)^+$ = 533	3402 (NH); 1741, 1680, 1662 (C=O)	200-202
N1	B8	OEt	from N1-H, CDT and H-B8-OEt in THF	72			M^+ = 498/500 (Cl)	1736, 1664 (C=O)	colourless crystals
N2	B2	OMe	from N2-H, CDT and H-B2-OMe*HCl and DIEA in THF	96	D	0.76	ESI: $(M-H)^-$ = 620 / 622 / 624 (Br_2); $(M+Na)^+$ = 644 / 646 / 648 (Br_2)	1728, 1664 (C=O)	colourless crystals

Example A3

Ethyl 2-[(3,5-dibromo-4-fluoro-phenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-(ethoxycarbonyl)-4-oxobutanoate

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The mixture of 4.39 g (0.019 mol) 3,4-dihydro-3-(4-piperidinyl)-2(1*H*)-quinazolinone, 9.25 g (0.019 mol) β,β-bis-(ethoxycarbonyl)-3,5-dibromo-4-fluoro-benzenebutanoic acid, 6.08 g (0.019 mol) TBTU, 6.9 ml (0.05 mol) triethylamine, 200 ml THF and 70 ml DMF was stirred overnight at room temperature. The solvents were eliminated in vacuo and the residue combined with dichloromethane and 10% aqueous citric acid solution. The organic phase was separated off, extracted with sodium hydrogen carbonate

solution and dried over sodium sulphate. After elimination of the desiccant and solvent the residue was combined with tert-butylmethylether and the precipitated solid substance was suction filtered. 11.0 g (83% of theory) of the desired product were obtained, mp = 167-170°.
IR (KBr): 1734, 1662 (C=O) cm^{-1}
ESI-MS: $(M+H)^+$ 696/698/700 (Br_2)

The following compounds of general formula N-B-C were prepared analogously:

N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
N1	B15[α-CO_2Et]	OEt	from N1-H, HO_2C-B15[α-CO_2Et]-OEt, TBTU, HOBt and NEt_3 in THF/DMF 220/70 v/v	89	AcOEt	0.7		1734, 1666 (C=O)	colourless crystals
N1	B16[α-CO_2Et]	OEt	from N1-H, HO_2C-B16[α-CO_2Et]-OEt, TBTU and NEt_3 in THF/DMF 150/50 v/v	72	AcOEt	0.33	ESI: $(M+H)^+$ = 628/630 (Br)	1739, 1653 (C=O)	189-191
N1	B20[α-CO_2Et]	OEt	from N1-H, HO_2C-B20[α-CO_2Et]-OEt, TBTU, HOBt and DIEA in THF/H_2O 10/1 v/v	100	D	0.73	M^+ = 657	1736, 1668, 1649 (C=O)	colourless viscous oil

N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
N1	B22[α-CO_2Et]	OEt	from N1-H, HO_2C-B22[α-CO_2Et]-OEt, TBTU, HOBt and DIEA in THF/H_2O 10/1 v/v	88	D	0.78		1734, 1668 (C=O)	colourless crystals
N1	B25[α-CO_2Et]	OEt	from N1-H, HO_2C-B25[α-CO_2Et]-OEt, TBTU, HOBt and DIEA in THF/H_2O 10/1 v/v	83	AcOEt	0.55	M^+ = 667/669/671/673 ($BrCl_2$)	1728, 1664, 1645 (C=O)	colourless viscous oil
N1	B27[α-CO_2Et]	OEt	from N1-H, HO_2C-B27[α-CO_2Et]-OEt, TBTU and NEt_3 in THF/DMF 250/10 v/v	88	AcOEt	0.56		1732, 1668 (C=O)	colourless crystals
N1	B29[α-CO_2Et]	OEt	from N1-H, HO_2C-B29[α-CO_2Et]-OEt, TBTU, HOBt and DIEA in THF/H2O 10/1 v/v	87	D	0.79		1753, 1728, 1660 (C=O)	
N1	B21[α-CO_2Et]	OEt	from N1-H, HO_2C-B21[α-CO_2Et]-OEt, TBTU, HOBt and DIEA in THF/H2O 10/1 v/v	75	D	0.74			colourless crystals

N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
N1	B30[α-CO_2Et]	OEt	from N1-H, HO_2C-B30[α-CO_2Et]-OEt, TBTU, HOBt and DIEA in THF/H2O 10/1 v/v	93	F	0.90	ESI: $(M+H)^+$ = 678/680/682 (Br_2)		colourless crystals
N1	B23	OMe	from N1-H, HO_2C-B23-OMe, TBTU, HOBt and NEt_3 in THF	100					
N1	B24[α-CO_2Et]	OEt	from N1-H, HO_2C-B24[α-CO_2Et]-OEt, TBTU, HOBt and DIEA in THF/H2O 10/1 v/v	95	D	0.82			colourless crystals
N6	B21[α-CO_2Et]	OEt	from N6-H, HO_2C-B21[α-CO_2Et]-OEt, TBTU, HOBt and NEt_3 in THF/DMF 5/1 v/v	86	AcOEt	0.9	M^+ = 727/729/731 (Br_2)	1734 (C=O)	colourless viscous oil

Example A4

(*R*,*S*)-3,4-dibromo-phenylalanine ethyl ester

The mixture of 37.40 g (0.140 mol) *N*-(diphenylmethylene)-glycine ethyl ester, 55.0 g (0.167 mol) (3,4-dibromophenyl)-methylbromide, 6.40 g (0.020 mol) tetrabutylammonium bromide, 57.80 g (0.35 mol) potassium carbonate sesquihydrate and 1000 ml acetonitrile was refluxed for 15 hours. The solid

was filtered off, the mother liquor was concentrated by evaporation in vacuo. The residue was taken up in 400 ml diethyl ether and after the addition of 200 ml semiconcentrated hydrochloric acid stirred for 1 hour at room temperature. The organic phase was separated off, the aqueous phase was washed twice more with 50 ml diethyl ether, then neutralised with solid sodium hydrogen carbonate while being cooled externally with ice and exhaustively extracted with ethyl acetate. The combined ethyl acetate extracts were dried over magnesium sulphate, filtered and evaporated down in vacuo. The product was obtained as a light brown oil.
Yield: 33.0 g (67% of theory). R_f 0.65 (El D).
IR (KBr): 1734 (C=O) cm^{-1}

The following compounds of general formula N-B-C were prepared analogously:

N	B	C	Remarks	% yield	El	R_f	MS	IR [cm^{-1}]	mp. [°C]
H	B6	OEt	from $Ph_2C{=}NCH_2CO_2Et$ and 3-Br-4,5-Me_2-C_6H_2-CH_2Br	60			ESI: $(M+H)^+$ = 300/302 (Br)	1738 (C=O)	colourless oil
H	B7	OEt	from $Ph_2C{=}NCH_2CO_2Et$ and 3,5-Br_2-4-Me-C_6H_2-CH_2Br	60	P	0.75		1738 (C=O)	colourless oil
H	B4	OEt	from $Ph_2C{=}NCH_2CO_2Et$ and 3,5-Cl_2-4-Me-C_6H_2-CH_2Br	70	B	0.73	ESI: $(M+H)^+$ = 276/278/280 (Cl_2)	1728 (C=O)	colourless crystals, mp. 44-46
H	B8	OEt	from $Ph_2C{=}NCH_2CO_2Et$ and 3-Cl-4-Me-C_6H_3-CH_2Cl	83	O	0.46		1736 (C=O)	

Example A5

(*R,S*)-3,4-difluorophenylalanine methyl ester hydrochloride

4.0 ml saturated methanolic hydrogen chloride solution were added to a suspension of 0.5 g (2.485 mmol) of 3,4-difluorophenylalanine in 10 ml of methanol and the mixture was stirred for 4 hours at room temperature. It was then evaporated down in vacuo, another 10 ml of methanol were added to the residue and the solvent was distilled off again in vacuo. 0.6 g (96% of theory) of colourless crystals were obtained, R_f 0.7 (EI dichloromethane).
ESI-MS: $(M+H)^+ = 216$

Example A6

β,β-bis-(ethoxycarbonyl)-3,5-dibromo-4-fluoro-benzene-butanoic acid

70 ml trifluoroacetic acid were added dropwise to an ice-cooled solution of 13.1 g (0.037 mol) 1,1-dimethylethyl β,β-bis-(ethoxycarbonyl)-3,5-dibromo-4-fluoro-benzenebutanoate in 450 ml dichloromethane, the cooling was removed, the mixture was stirred overnight at ambient temperature and then evaporated down in vacuo. The residue was dried twice by coevaporation with petroleum ether, triturated with petroleum ether, suction filtered and dried in vacuo. 9.3 g (79% of theory) of colourless crystals were obtained.
IR (KBr): 1707 (C=O) cm^{-1}
ESI-MS : $(M-H)^- = 481/483/485$ (Br_2)

The following compounds of general formula N-B-C were prepared analogously:

N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
HO	B15[α-CO2Et]	OEt	from $(H_3C)_3CO_2C$-B15[α-CO_2Et]-OEt and TFA in CH_2Cl_2	81	V	0.1		1709 (C=O)	
HO	B16[α-CO2Et]	OEt	from $(H_3C)_3CO_2C$-B16[α-CO_2Et]-OEt and TFA in CH_2Cl_2	100				1738 (C=O)	colourless viscous oil
HO	B20[α-CO2Et]	OEt	from $(H_3C)_3CO_2C$-B20[α-CO_2Et]-OEt and TFA in CH_2Cl_2	77	V	0.24		3321 (OH); 1714 (C=O); 1161, 1124 (CF_3)	colourless crystals
HO	B22[α-CO2Et]	OEt	from $(H_3C)_3CO_2C$-B22[α-CO_2Et]-OEt and TFA in CH_2Cl_2	69	W	0.21		1736 (C=O)	colourless crystals
HO	B25[α-CO2Et]	OEt	from $(H_3C)_3CO_2C$-B25[α-CO_2Et]-OEt and TFA in CH_2Cl_2	72				1730, 1711 (C=O)	colourless viscous oil
HO	B27[α-CO2Et]	OEt	from $(H_3C)_3CO_2C$-B27[α-CO_2Et]-OEt and TFA in CH_2Cl_2	93				1736 (C=O)	
HO	B24[α-CO2Et]	OEt	from $(H_3C)_3CO_2C$-B24[α-CO_2Et]-OEt and TFA in CH_2Cl_2	68	X	0.28		1709 (C=O)	colourless crystals
HO	B19[α-CO2Et]	OEt	from $(H_3C)_3CO_2C$-B19[α-CO_2Et]-OEt and TFA in CH_2Cl_2	46					
HO	B30[α-CO2Et]	OEt	from $(H_3C)_3CO_2C$-B30[α-CO_2Et]-OEt and TFA in CH_2Cl_2	81			ESI: $(M-H)^-$ = 463/465/467 (Br_2)		colourless crystals

N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
HO	B24[α-CO2Et]	OEt	from $(H_3C)_3CO_2C$-B24[α-CO_2Et]-OEt and TFA in CH_2Cl_2	54			ESI: $(M-H)^-$ = 375/377/379 (Cl_2)		colourless crystals

Example A7

1,1-dimethylethyl 3,5-dibromo-4-fluoro-β,β-bis-(ethoxycarbonyl)-benzenebutanoate

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0.64 g (0.0266 mol) 95% sodium hydride were added to the solution of 6.69 g (0.024 mol) diethyl [(1,1-dimethylethoxy-carbonyl)methyl]-malonate in 170 ml anhydrous tetrahydrofuran while cooling externally with ice water. After one hour's stirring a solution of 8.35 g (0.024 mol) 3,5-dibromo-4-fluorobenzylbromide in 30 ml of tetrahydrofuran was added dropwise thereto while maintaining a reaction temperature of 0 to +5 °C and the mixture was then allowed to come up to room temperature within 14 hours. The reaction mixture was freed from solvent in vacuo, the residue was combined with 200 ml 10% citric acid and exhaustively extracted with *tert.*-butylmethylether. After working up in the usual way the combined extracts yielded 13.1 g (100% of theory) of a colourless oil, R_f = 0.14 (EI Y), which was used in the next step without any purification.

IR (KBr): 1732 (C=O) cm^{-1}

ESI-MS: $(M+Na)^+$ = 561/563/565 (Br_2)

The following compounds of general formula N-B-C were prepared analogously:

N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
Me_3CO	B15[α-CO2Et]	OEt	from $(H_3C)_3COCO$-$CH_2C(CO_2Et)_2$, 3,4,5-Me_3-$C_6H_2CH_2Br$ and NaH in THF	100	V	0.6			colourless oil
Me_3CO	B16[α-CO2Et]	OEt	from $(H_3C)_3COCO$-$CH_2C(CO_2Et)_2$, 3Br-4,5-Me_2-$C_6H_2CH_2Br$ and NaH in THF	67	CH_2Cl_2	0.71		1736 (C=O)	colourless oil
Me_3CO	B20[α-CO2Et]	OEt	from $(H_3C)_3COCO$-$CH_2C(CO_2Et)_2$, 2,4-$(CF_3)_2$-$C_6H_3CH_2Br$ and NaH in THF	100	V	0.72	no M^+; $(M-C_4H_8)^+$ = 444	1736 (C=O)	
Me_3CO	B22[α-CO2Et]	OEt	from $(H_3C)_3COCO$-$CH_2C(CO_2Et)_2$, 3,4,5Br_3-$C_6H_2CH_2Br$ and NaH in THF	91	W	0.78		1734 (C=O)	colourless oil
Me_3CO	B25[α-CO2Et]	OEt	from $(H_3C)_3COCO$-$CH_2C(CO_2Et)_2$, 4-Br-3,5Cl_2-$C_6H_2CH_2Br$ and NaH in THF	100	Y	0.75			colourless viscous oil
Me_3CO	B27[α-CO2Et]	OEt	from $(H_3C)_3COCO$-$CH_2C(CO_2Et)_2$, 3,4-$(CH_2)_2O$-$C_6H_3CH_2Br$ and NaH in THF	58	Y	0.31	M^+ = 406	1734 (C=O)	

N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
Me_3CO	B29[α-CO2Et]	OEt	from $(H_3C)_3COCO$-$CH_2C(CO_2Et)_2$, $2,3Cl_2$-$C_6H_3CH_2Cl$ and NaH in THF	89	X	0.49		1736 (C=O)	colourless oil
Me_3CO	B19[α-CO2Et]	OEt	from $(H_3C)_3COCO$-$CH_2C(CO_2Et)_2$, $4NH_2$-$3,5Cl_2$-$C_6H_2CH_2Br$ and NaH in THF	88					colourless oil

Example A8

3,4-dimethoxy-β-(methoxycarbonyl)-benzenebutanoic acid

The solution of 58.0 g (0.205 mol) 4-[(3,4-dimethoxyphenyl]-3-(methoxycarbonyl)-3-butenoic acid in 500 ml of methanol was hydrogenated at 5 bar hydrogen in the presence of 3.0 g 10% platinum/activated charcoal until the uptake of hydrogen had ended. After working up in the usual way 26.0 g (46% of theory) of colourless crystals were obtained, mp = 104-107°C

The following compound of general formula N-B-C was obtained analogously:

N	B	C	Remarks	% yield	EI	R_f	mp. [°C]
HO	B26	OMe	from 4-(2-naphthyl)-3-(methoxycarbonyl)-3-butenoic acid, H_2 and Pd-C in MeOH		X	0.85	

Example A9

4-[(3,4-dimethoxy-phenyl]-3-(methoxycarbonyl)-3-butenoic acid

26.6 ml (0.2 mol) dimethyl succinate were added to a freshly prepared solution of 4.6 g (0.2 mol) sodium in 250 ml anhydrous methanol and after one hour's stirring at room temperature the solution of 33.3 g (0.2 mol) 3,4-dimethoxybenzaldehyde in 100 ml anhydrous methanol was added dropwise. Then the mixture was refluxed for 6 hours, the methanol was eliminated in vacuo and the bottom remaining was maintained at a reaction temperature of 80°C for 30 minutes. The viscous slurry obtained was taken up in 500 ml of water, acidified with 20% aqueous citric acid solution and the resulting mixture was exhaustively extracted with ethyl acetate. The combined ethyl acetate extracts were in turn extracted five times with 5% aqueous ammonia solution. The ammoniacal extracts were carefully acidified with 20% aqueous citric acid solution and then exhaustively extracted with ethyl acetate. These extracts were washed with water, dried over sodium sulphate and freed from the solvent in vacuo. The crude product (quantitative yield) was further reacted without purification.

The following compounds of general formula N-B-C were obtained analogously:

N	B	C	Remarks	% yield	EI	R_f
4-(2-naphthyl)-3-(methoxycarbonyl)-3-butenoic acid			from 2-naphthaldehyde, dimethyl succinate and NaOMe in MeOH	65	X	0.8

Example A10

Methyl [1,4']bipiperidinyl-4-acetate

The solution of 0.669 g (2.024 mmol) of methyl 1'-phenylmethyl-[1,4']bipiperidinyl-4-acetate in 20 ml of methanol was hydrogenated at a pressure of 5 bar after the addition of 100 mg of 10% palladium on charcoal until the uptake of hydrogen had ended. The catalyst was filtered off, the filtrate was freed from solvent, the residue was taken up in 20 ml THF, the solution obtained was filtered and evaporated down again. The residue was used without further purification. Colourless oil. Yield: 490 mg (100% of theory).

ESI-MS: $(M+H)^+ = 241$

$(M+Na)^+ = 253$

The following compounds of general formula N-B-C were prepared analogously:

N	B	C	Remarks	% yield	EI	R_f	MS	mp. [°C]
H	-	C5	from $PhCH_2$-C5, H_2 and Pd/C in MeOH	100	G	0.22	ESI: $(M+H)^+$ = 241; $(M+Na)^+$ = 253	colourless oil
H	-	C12	from $PhCH_2$-C12, H_2 and Pd/C in EtOH	98	D	0.17	ESI: $(M+H)^+$ = 284	colourless crystals
H	-	C9	from $PhCH_2$-C9, H_2 and Pd/C in EtOH	78	O	0.1		colourless oil
H	-	C3	from $PhCH_2$-C3, H_2 and Pd/C in MeOH	99			ESI: $(M+H)^+$ = 284; $(M+Na)^+$ = 306	colourless oil
H	-	C1	from $PhCH_2$-C1, H_2 and Pd/C in EtOH	97	M	0.38	ESI: $(M+H)^+$ = 256	
H	-	C14	from $PhCH_2$-C14, H_2 and Pd/C in MeOH	79	G	0.14	ESI: $(M+H)^+$ = 213	colourless crystals

N	B	C	Remarks	% yield	EI	R_f	MS	mp. [°C]
H	-	C16	from $PhCH_2$-C16, H_2 and Pd/C in MeOH	67	G	0.16	ESI: $(M+H)^+$ = 213	colourless crystals
H	-	C19	from $PhCH_2$-C19, H_2 and Pd/C in MeOH	100	G	0.20	ESI: $(M+H)^+$ = 227	colourless oil
H	-	C22	from $PhCH_2$-C22, H_2 and Pd/C in MeOH	100	C	0.06	ESI: $(M+H)^+$ = 227	colourless crystals
H	-	C26	from $PhCH_2$-C26, H_2 and Pd/C in MeOH	100				colourless crystals
H	-	C28	from methyl 4-[(1-phenylmethyl)-1,2,3,6-tetrahydro-4-pyrididinyl]-benzoate, H_2 and Pd/C in MeOH	70	S	0.4		colourless crystals
H	-	C18	acetate, from $PhCH_2$-C18, H_2 and Pd/C in MeOH	88	G	0.20	ESI: $(M+H)^+$ = 227	colourless viscous oil
H	-	C7	from $PhCH_2$-C7, H_2 and Pd/C in EtOH	92	O	0.15	ESI: $(M+H)^+$ = 241; $(M+Na)^+$ = 263	colourless oil
H	-	C50	from $PhCH_2$-C50, H_2 and $Pd(OH)_2$ (Pearlman's catalyst) in EtOH	100	KK	0.21	ESI: $(M+H)^+$ = 256	colourless viscous oil
ethyl 4-methyl-2-piperazine-carboxylate			from ethyl 1-(phenylmethyl)-4-methyl-2-piperazinecarboxylate, H_2 and $Pd(OH)_2$ (Pearlman's catalyst) in EtOH	99				colourless oil
H	-	C46	from $PhCH_2$-C46, H_2 and $Pd(OH)_2$ (Pearlman's catalyst) in EtOH	100	DD	0.24	ESI: $(M+H)^+$ = 256	colourless viscous oil

N	B	C	Remarks	% yield	EI	R_f	MS	mp. [°C]
H	-	C45	from $PhCH_2$-C45, H_2 and $Pd(OH)_2$ (Pearlman's catalyst) in EtOH	100	LL	0.1	ESI: $(M+H)^+$ = 256	colourless oil
ethyl 2-piperazine-carboxylate			from ethyl 1,4-bis-(phenylmethyl)-2-piperazinecarboxylate, H_2 and 10% Pd/C in EtOH	100	MM	0.2	ESI: $(M+H)^+$ = 159	

Example A11

Methyl 1'-(phenylmethyl)-[1,4']bipiperidinyl-4-acetate

4.0 ml glacial acetic acid and 20 g of molecular sieve 3 Å were added to a mixture of 4.549 ml (24.54 mmol) of 1-(phenylmethyl)-4-piperidinene, 4.753 g (24.54 mmol) of methyl 4-piperidineacetate hydrochloride and 40 ml of THF, the mixture was stirred for 2 hours at room temperature, cooled to 0 °C and while this temperature was maintained a total of 6.358 g (30.0 mmol) of sodium triacetoxyborohydride were added in small batches within 8 hours. Then the resulting mixture was stirred for another 16 hours at room temperature. The mixture was made alkaline with sodium hydrogen carbonate, extracted exhaustively with ethyl acetate, the combined extracts were dried over sodium sulphate and the evaporation residue was chromatographed on silica gel using first 30/1 dichloromethane/methanol, then 20/1, and finally 10/1 as eluants. Working up the appropriate fractions yielded 1.804 g (22% of theory) of a readily mobile oil which set overnight into colourless crystals. R_f =0.56 (EI B).
ESI-MS: $(M+H)^+$ = 331.

The following compounds of general formula N-B-C were prepared analogously:

N	B	C	Remarks	% yield	EI	R_f	MS	mp. [°C]
$PhCH_2$	-	C7 + C9	from 1-(phenylmethyl)-piperazine, ethyl 4-oxocyclohexane-carboxylate and $Na(CN)BH_3$/AcOH in MeOH at pH 5-6; separation of the two diastereomers on silica gel, EI dichloromethane / MeOH 30/1 v/v	cis: 14.7 + trans: 13.8 + cis / trans: 5.8	AA	cis: 0.40; trans: 0.30	cis: ESI: $(M+H)^+$ = 331; $(M+Na)^+$ = 353; trans: ESI: $(M+H)^+$ = 331	colour-less liquids
$PhCH_2$	-	C3	from 1-(phenylmethyl)-piperazine, 1,1-dimethylethyl 4-oxo-1-piperidineacetate and $Na(CN)BH_3$/AcOH in MeOH at pH 5-6	58	O	0.67	ESI: $(M+H)^+$ = 374; $(M+Na)^+$ = 396	colour-less crystals
4-[1-(phenylmethyl)-4-piperidinyl]-1-(1,1-dimethylethoxycarbonyl)-piperazine			from 1-(phenylmethyl)-4-piperidinene, 1-(1,1-dimethylethoxycarbonyl)-piperazine and $NaBH(OAc)_3$/AcOH in THF	100	D	0.60	ESI: $(M+H)^+$ = 360; $(M+Na)^+$ = 382; $(2M+Na)^+$ = 741	colour-less oil
$PhCH_2$	-	C14	from 1-(phenylmethyl)-4-piperidinene, L-proline methyl ester hydrochloride and $NaBH(OAc)_3$/AcOH in THF	51	G	0.50	ESI: $(M+H)^+$ = 303	colour-less oil

N	B	C	Remarks	% yield	El	R_f	MS	mp. [°C]
$PhCH_2$	-	C16	from 1-(phenylmethyl)-4-piperidinene, D-proline methyl ester hydrochloride and $NaBH(OAc)_3$/AcOH in THF	54	G	0.50	ESI: $(M+H)^+$ = 303; $(M+Na)^+$ = 325	colour-less oil
$PhCH_2$	-	C19	from 1-(phenylmethyl)-4-piperidinene, L-homoproline methylester hydrochloride [Bachem] and $NaBH(OAc)_3$ in CH_2Cl_2	51	G	0.40	ESI: $(M+H)^+$ = 317; $(M+Na)^+$ = 339	colour-less oil
$PhCH_2$	-	C18	from 1-(phenylmethyl)-4-piperidinene, D-homoproline methylester hydrochloride [Bachem] and $NaBH(OAc)_3$ in CH_2Cl_2	57	G	0.40	ESI: $(M+H)^+$ = 317	colour-less viscous oil
$PhCH_2$	-	C50	from 1-(phenylmethyl)-4-piperidinene, ethyl 4-methyl-2-piperazinecarboxylate and $NaBH(OAc)_3$ in THF	22	DD	0.84	ESI: $(M+H)^+$ = 346	'
$PhCH_2$	-	C46	from 1-methyl-4-piperidinene, ethyl bis-(trifluoroacetate) 1-(phenylmethyl)-2-piperazinecarboxylate - and $NaBH(OAc)_3$ in THF	100	C	0.53	ESI: $(M+H)^+$ = 346	colour-less oil

N	B	C	Remarks	% yield	EI	R_f	MS	mp. [°C]
$PhCH_3$	-	C45	from 1-(phenylmethyl)-4-piperidinene, ethyl bis-(trifluoroacetate) 1-methyl-2-piperazinecarboxylate and $NaBH(OAc)_3$ in THF	100	C	0.41	$M^+ = 345$	colour-less oil
Boc	-	C44	from 1-methyl-4-piperidinene, ethyl -bis-(trifluoroacetate) 4-(1,1-dimethylethoxycarbonyl)-2-piperazinecarboxylate and $NaBH(OAc)_3$ in THF	57	C	0.46	ESI: $(M+H)^+ = 356$	colour-less viscous oil

Example A12

Ethyl 4-[1-(phenylmethyl)-4-piperidinyl]-1-piperazineacetate

3.5 ml (19.892 mmol) of DIEA were added to a suspension of 2.0 g (3.325 mmol) of 1-(phenylmethyl)-4-(1-piperazinyl)-piperidine-tris-(trifluoroacetate) in 50 ml dichloromethane and the mixture was stirred for 10 minutes at room temperature. Then 0.38 ml (3.365 mmol) of ethyl bromoacetate were added and the mixture was stirred overnight at room temperature. The reaction mixture was extracted four times with 50 ml of water, dried over sodium sulphate and concentrated by evaporation. 0.70 g (61% of theory) of the desired product were obtained, R_f 0.63 (El D) and
ESI-MS: $(M+H)^+ = 346$.

The following compound of general formula N-B-C was obtained analogously:

N	B	C	Remarks	% yield	EI	R_f	MS	mp. [°C]
$PhCH_2$	-	C12	from 1-(phenylmethyl)-4-(1-piperazinyl)-piperidine-tris-(trifluoroacetate), 1,1-dimethylethyl bromoacetate and K_2CO_3 in CH_3CN	65	D	0.51	ESI: $(M+H)^+$ = 374; $(M+Na)^+$ = 396	colourless crystals

Example A13

1-(phenylmethyl)-4-(1-piperazinyl)-piperidine-tris-(trifluoroacetate)

The mixture of 77.6 g (0.216 mol) 4-[1-(phenylmethyl)-4-piperidinyl]-1-(1,1-dimethylethoxycarbonyl)-piperazine, 150 ml (1.941 mol) trifluoroacetic acid and 450 ml dichloromethane was refluxed for 1 hour and then stirred for 2 hours at room temperature. The solvent was distilled off, the residue triturated with diethyl ether, suction filtered and dried in the air. 119.0 g (92% of theory) of colourless crystals were obtained, R_f 0.20 (EI D) and
ESI-MS: $(M+H)^+$ = 260

The following compounds of general formula N-B-C were prepared analogously:

N	B	C	Remarks	% yield	EI	R_f	MS	mp. [°C]
H	-	C29	from ethyl 4-[[1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl]methyl]-benzoate and TFA in CH_2Cl_2	89	BB	0.70		colourless crystals
H	-	C44	from ethyl 4-(1,1-dimethylethoxycarbonyl)-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylate and TFA in CH_2Cl_2	100	DD	0.11	M^+ = 255	colourless viscous oil
ethyl-bis-(trifluoroacetate) 1-(phenylmethyl)-2-piperazine-carboxylate			from ethyl 4-(1,1-dimethylethoxycarbonyl)-1-(phenylmethyl)-2-piperazinecarboxylate and TFA in CH_2Cl_2	100	AcOEt	0.00	ESI: $(M+H)^+$ = 249	colourless oil
ethyl-bis-(trifluoroacetate)1-methyl-2-piperazine-carboxylate			from ethyl 4-(1,1-dimethylethoxycarbonyl)-1-methyl-2-piperazinecarboxylate and TFA in CH_2Cl_2	100	DD	0.16	ESI: $(M+H)^+$ = 173	colourless viscous oil

Example A14

methyl 1'-(phenylmethyl)-[1,4']bipiperidinyl-4'-carboxylate

1.124 g (3.5 mmol) of TBTU and 1.0 ml (7.175 mmol) of triethylamine were added to the solution of 1.0 g (3.307 mmol) of 1'-(phenylmethyl)-[1,4']bipiperidinyl-4'-carboxylic acid in 30 ml DMF, the mixture was stirred for 20 minutes at room temperature, then 20 ml of methanol were added and the mixture was stirred for a further 3 hours at ambient temperature. The mixture was concentrated by evaporation, the residue was taken up in 50 ml of ethyl acetate and filtered. The filtrate was evaporated down, the residue purified by

column chromatography on silica gel, initially using ethyl acetate, then ethyl acetate mixed with up to 5% methanol/conc. ammonia (9/1 v/v) as eluant. 0.231 g (22% of theory) of colourless crystals were obtained, mp. 84.7 °C and Rf 0.73 (El F).
ESI-MS: $(M+H)^+$ = 317

Example A15

Methyl 3-(4-piperidinyl)-benzoate -hydrochloride

The mixture of 500 mg (2.069 mmol) of 3-(4-piperidinyl)-benzoic acid-hydrochloride and 10 ml saturated methanolic hydrogen chloride solution was stirred overnight at room temperature. The reaction mixture was concentrated by evaporation in vacuo, the residue was stirred with 3 ml isopropanol, suction filtered, washed with diethyl ether and dried at 60°C in the circulating air dryer. 390 mg (74% of theory) of colourless crystals were obtained, R_f 0.34 (El D).
IR (KBr): 1728 (C=O) cm^{-1}
ESI-MS: $(M+H)^+$ = 220;
$(M+Cl+HCl)^-$ = 290/292/294 (Cl_2)

The following esters of general formula N-B-C were obtained analogously:

N	B	C	Remarks	% yield	El	R_f	MS	IR [cm^{-1}]	mp. [°C]
H	-	C31	dihydrochloride; from H-C38 [BAYER], MeOH and HCl	76	D	0.58	ESI: $(M+H)^+$ = 289; $(M+Cl+HCl)^-$ = 359/361/363 (Cl_2)	1722 (C=O)	colour-less crystals
$PhCH_2$	-	C41	from $PhCH_2$-C43, MeOH and HCl	52	D	0.88	ESI: $(M+H)^+$ = 318; $(M+Na)^+$ = 340; $(2M+Na)^+$ = 657		

N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
methyl 2-aminothiazole-5-carboxylate hydrochloride			from 2-aminothiazole-5-carboxylic acid, MeOH and HCl	100	D	0.59	ESI: $(M+H)^+$ = 159; $(M-H)^-$ = 157		
methyl 4-[1-(phenylmethyl)-1,2,3,6-tetrahydro-4-pyridinyl]-benzoate			from 4-[1-(phenylmethyl)-1,2,3,6-tetrahydro-4-pyridinyl]-benzoic acid, MeOH and HCl	85			ESI: $(M+H)^+$ = 308	1707 (C=O)	

Example A16

1'-(phenylmethyl)-[1,4']bipiperidinyl-4'-carboxylic acid

A total of 5.0 g (17.642 mmol) of 1'-(phenylmethyl)-[1,4']bipiperidinyl-4'-carbonitrile were added in small batches to 15 ml of conc. sulphuric acid. After the nitrile had dissolved, the mixture was stirred for a further 3 hours at room temperature, then 10 ml of water were added and the mixture was refluxed for 15 hours. The cooled mixture was stirred into 50 ml ice water and adjusted to pH 7 with conc. ammonia. The precipitate was suction filtered, washed with a little water, stirred with 10 ml dichloromethane, suction filtered again, then dried in vacuo. 1.56 g (29% of theory) of colourless crystals were obtained, Rf 0.0 (EI DD).
ESI-MS: (M+H) = 303

Example A17

Ethyl 3-(1-piperazinyl)-benzoate

30 ml of a saturated solution of hydrogen bromide in glacial acetic acid was added dropwise at room temperature to the solution of 18.5 g (0.055 mol) ethyl 3-[4-(phenylmethoxycarbonyl)-1-piperazinyl]-benzoate in 30 ml glacial

acetic acid and stirred for a further 4 hours at room temperature. 300 ml diethyl ether were added to the mixture, the precipitate formed was then suction filtered, washed thoroughly with diethyl ether and dried in the air. Yield 17.8 g (82% of theory). Colourless crystals, mp. 226 °C (Z) and R_f 0.24 (El EE).

$C_{13}H_{18}N_2O_2$*2 HBr (396.13)

Calc.:	C 39.42	H 5.09	N 7.07	Br 40.34
Found:	39.27	5.06	7.15	40.35

Example A18

Ethyl 3-[4-(phenylmethoxycarbonyl)-1-piperazinyl]-benzoate

At intervals of 16 hours 15.0 g (a total of 0.176 mol) of benzyl chlorocarbonate were added twice to the solution of 26.0 g (0.08 mol) ethyl 3-[4-(phenylmethyl)-1-piperazinyl]-benzoate in 260 ml dichloromethane and the mixture was stirred for a total of 32 hours at room temperature. The solvent was eliminated in vacuo, the residue purified by column chromatography on silica gel using dichloromethane as eluant. 18.8 g (70% of theory) of a colourless oil were obtained, R_f 0.67 (El FF).

Example A19

Ethyl 3-[4-(phenylmethyl)-1-piperazinyl]-benzoate -hydriodide

The mixture of 53.6 g (0.2 mol) *N,N*-bis-(2-chlorethyl)-benzenemethanamine-hydrochloride, 40.2 g (0.2 mol) ethyl 3-aminobenzoate -hydrochloride, 30.0 g (0.2 mol) sodium iodide, 20.0 g sodium carbonate and 1 l of n-propanol was refluxed for 2 hours. The mixture was cooled to 80°C, a further 15 g of sodium carbonate were added slowly and the mixture was refluxed for another 2 hours. After cooling to 80°C the remaining sodium carbonate from a total amount of 53.0 g (0.5 mol) was added and again the mixture was refluxed for 2 hours. It was left to cool, the insoluble salts were filtered off and the filtrate

was evaporated down in vacuo. The residue was taken up in 200 ml dichloromethane, the dichloromethane solution was washed twice with 50 ml 1N hydrochloric acid, then concentrated by evaporation. After being recrystallised from ethanol the residue remaining yielded 43.0 g (48% of theory) of colourless crystals, mp. 180-182 °C and R_f = 0.62 (El GG).

Example A20

4-[1-(phenylmethyl)-1,2,3,6-tetrahydro-4-pyridinyl]-benzoic acid

25.0 ml (0.04 mol) of a 1.6-molar solution of *n*-butyl lithium in *n*-hexane were added dropwise to the solution of 13.13 g (0.040 mol) 4-(4-bromophenyl)-1-(phenylmethyl)-1,2,3,6-tetrahydropyridine in 190 ml of anhydrous THF under an argon atmosphere and while maintaining a reaction temperature of -70 to -60 °C. After 30 minutes at -60°C the mixture was poured, while stirring well, onto 500 g of finely crushed dry ice and the mixture was then left overnight to come up to room temperature. It was diluted with 300 ml diethyl ether and then extracted twice with 100 ml of water. While cooling externally, the combined aqueous extracts were adjusted to pH 7.5 with 2N hydrochloric acid. The precipitate formed was suction filtered, stirred with 50 ml hot methanol and after cooling suction filtered again. After drying in the desiccator 8.3 g (71% of theory) of colourless crystals were obtained, R_f 0.5 (El HH).
ESI-MS: $(M+H)^+$ = 294
$(M-H)^-$ = 292

Example A21

4-(4-Bromophenyl)-1-(phenylmethyl)-4-piperidinel

62.5 ml (0.1 mol) of a 1.6 molar solution of *n*-butyl lithium in *n*-hexane were added dropwise to the solution of 23.591 g (0.10 mol) 1,4-dibromobenzene in 250 ml anhydrous THF while maintaining a reaction temperature of -60 to -50 °C. The mixture was stirred for a further 20 minutes at the stated temperature

before the solution of 18.926 g (0.10 mol) 1-(phenylmethyl)-4-piperidinene in 50 ml anhydrous THF was added dropwise. The mixture was allowed to warm up to room temperature, then stirred overnight at this temperature, the mixture was then added to ice water and exhaustively extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water and saturated saline solution, dried over sodium sulphate and concentrated by evaporation in vacuo. The residue was recrystallised from diisopropylether. 23.1 g (67% of theory) of colourless crystals were obtained, R_f 0.4 (El BB).

Example A22

Ethyl 4-[[1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl]methyl]-benzoate

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The solution of 38.7 g (0.112 mol) 1-(1,1-dimethylethoxycarbonyl)-4-[4-(ethoxycarbonyl)-phenylmethylene]-piperidine in 350 ml of ethyl acetate was hydrogenated at room temperature and under a pressure of 5 bar in the presence of 4.82 g 10% palladium on charcoal until the uptake of hydrogen had ended. Working up in the usual way yielded 35.8 g (92% of theory) of a colourless oil which was used without any further purification.

Example A23

1-(1,1-dimethylethoxycarbonyl)-4-[4-(ethoxycarbonyl)-phenylmethylene]-piperidine

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85.0 ml (0.136 mol) of a 1.6 molar solution of *n*-butyl lithium in *n*-hexane was added dropwise to the solution of 19.2 ml (0.135 mol) diisopropylamine in 400 ml anhydrous THF using argon as protective gas and while maintaining a reaction temperature of -20 to -10 °C. This temperature was maintained for another 20 minutes and then the solution of 39.35 g (0.131 mol) diethyl [4-(ethoxycarbonyl)phenyl]-methanephosphonate in 100 ml THF was added dropwise. The mixture was stirred for a further 20 minutes at a temperature between -20 and -10 °C, then the solution of 28.1 g (0.131 mol) 1-(1,1-

dimethylethoxy-carbonyl)-4-piperidinene in 100 ml THF was added dropwise thereto and the mixture was left overnight to warm up to room temperature. The mixture was stirred into ice water, the resulting mixture was exhaustively extracted with ethyl acetate, the combined extracts were washed with saturated aqueous NaCl solution, dried over sodium sulphate and freed from solvent. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate 7/1 v/v as eluant. 38.7 g (86% of theory) of a colourless oil were obtained, which solidified in the presence of petroleum ether to form colourless crystals.

Example A24

Diethyl [4-(ethoxycarbonyl)phenyl]-methanephosphonate

55 ml (0.316 mol) triethyl phosphite were placed in a stirring apparatus and pre-heated to an internal temperature of 90°C. The suspension of 60.0 g (0.247 mol) ethyl 4-(bromomethyl)-benzoate in 100 ml dichloromethane was slowly added thereto in small batches, while the ethyl bromide formed and the evaporating dichloromethane were continuously distilled off. Once the quantity of ethyl bromide formed had significantly diminished, the reaction temperature was slowly increased to 140°C and this temperature was maintained until the formation of ethyl bromide had ended (approx. 2 hours). The excess triethyl phosphite was eliminated in vacuo, the residue was suspended in a little ethyl acetate and purified by column chromatography on silica gel using ethyl acetate/petroleum ether (gradient 1/1 → 1/0 v/v) as eluant. After working up in the usual way 56.3 g (76% of theory) of the above title compound were obtained in the form of a colourless oil.

Example A25

Ethyl 4-[2-(4-piperidinyl)ethyl]-benzoate

The solution of 22.0 g (0.076 mol) ethyl 4-[2-(4-pyridinyl)vinyl]-benzoate hydrochloride in 800 ml of ethanol was hydrogenated in the presence of 2 g platinum(IV)-oxide at 3.8 bar hydrogen pressure for 8 hours. Catalyst and solvent were removed, the residue was taken up in 5% hydrochloric acid and extracted twice with 50 ml diethyl ether. The aqueous phase was made alkaline with sodium hydroxide and exhaustively extracted with ethyl acetate. The combined ethyl acetate extracts were washed with saturated saline solution, dried over sodium sulphate and concentrated by evaporation. The oily product obtained (17.0 g, 86% of theory) was used without further purification.

Example A26

Ethyl (*E*)-4-[2-(4-pyridinyl)vinyl]-benzoate hydrochloride

A solution of 9.1 g (85.0 mmol) of 4-pyridine-carboxaldehyde and 25.0 g (83.3 mmol) of diethyl [4-(ethoxycarbonyl)phenyl]-methanephosphonate in 150 ml THF was added dropwise to a suspension of 1.87 g (78 mmol) of sodium hydride in 150 ml THF while maintaining a reaction temperature of -10 to 0°C. The mixture was stirred for 35 hours under a nitrogen atmosphere. Then it was distributed between water and diethyl ether, the ethereal phase was dried over sodium sulphate, evaporated down to a volume of approx. 200 ml and combined with ethereal hydrogen chloride solution until the reaction of precipitation had ended. The colourless crystals obtained were suction filtered, washed with diethyl ether and dried in the air.
Yield: 22.0 g (87% of theory). mp. 215-225 °C.

Example A27

Methyl 2-(1-piperazinyl)-thiazole-5-carboxylate

10.0 g (116.09 mmol) of anhydrous piperazine were added to a solution of 4.2 g (23.647 mmol) of methyl 2-chlorothiazole-5-carboxylate in 5 ml of ethanol and refluxed for 3 hours. The reaction mixture was combined with saturated aqueous sodium hydrogen carbonate solution and exhaustively extracted with ethyl acetate. The combined organic extracts were washed thoroughly with water, dried over sodium sulphate and concentrated by evaporation in vacuo. 1.8 g (34% of theory) of colourless crystals were obtained, R_f 0.44 (El D).

Example A28

Methyl 2-chlorothiazole-5-carboxylate

20 g of crushed ice were added to a suspension of 14.0 g (71.927 mmol) of methyl 2-aminothiazol-5-carboxylate hydrochloride in 8 ml of conc. hydrochloric acid and while cooling externally a solution of 5.0 g (72.464 mmol) of sodium nitrite in 30 ml of water was added dropwise, while the reaction temperature was kept below 0 °C at all times. After 30 minutes 7.2 g (72.735 mmol) of copper (I) chloride were added, the mixture was stirred for another hour while being cooled and in the following 1½ hours allowed to come slowly up to room temperature. The mixture was exhaustively extracted with diethyl ether, the combined extracts were washed with saturated saline solution, dried over sodium sulphate and evaporated down. 4.3 g (34% of theory) of a colourless oil were obtained, Rf = 0.94 (El D), which was used in the next steps without any further purification.
MS: M^+ = 177/179 (Cl)

Example A29

Methyl 2-(1-piperazinyl)-thiazole-4-carboxylate hydrochloride

4.0 ml (35.973 mmol) of 1-chloroethyl chloroformate were added to an ice-cooled solution of 8.0 g (15.752 mmol) of methyl 2-[4-(phenylmethyl)-1-piperazinyl]-thiazole-4-carboxylate in 60 ml of 1,2-dichloroethane, the mixture was stirred for another 20 minutes at 0 °C and refluxed overnight, before distilling off the solvent. The residue was combined with 60 ml of methanol and refluxed for another 4 hours. The solvent was eliminated in vacuo, the residue was triturated with 3 ml of methanol, then suction filtered. After drying in the vacuum drying cupboard 2.5 g (60% of theory) of colourless crystals were obtained, R_f = 0.49 (EI D).

ESI-MS: $(M+H)^+$ = 228;
$(M+Na)^+$ = 250

Example A30

2-[4-(phenylmethyl)-1-piperazinyl]-thiazole-4-carboxylic acid-hydrobromide

12.7 g (76.066 mmol) of bromopyruvic acid were added to the solution of 18.0 g (76.482 mmol) of 1-(aminothiocarbonyl)-4-(phenylmethyl)-piperazine in 300 ml of ethanol and refluxed for 3 hours. The mixture was left to stand overnight, the precipitated solid product was separated off by suction filtering and washed with ethanol. After drying 23.0 g (79% of theory) of colourless crystals were obtained, R_f 0.10 (EI D).

ESI-MS: $(M-H)^-$ = 302;
$(M+Na)^+$ = 326

Example A31

1-(aminothiocarbonyl)-4-(phenylmethyl)-piperazine

12.596 g (108.247 mmol) of *tert.*-butyl isothiocyanate were added dropwise to an ice-cooled solution of 19.08 g (108.25 mmol) of 1-(phenylmethyl)-piperazine in 150 ml dichloromethane, while keeping the reaction temperature below +5 °C. The mixture was stirred overnight at room temperature, freed from solvent and the residue remaining was boiled for 1½ hours with 100 ml of conc. hydrochloric acid. After cooling, it was neutralised while cooling externally with 12M sodium hydroxide solution and extracted exhaustively with dichloromethane. The combined dichloromethane extracts were dried over sodium sulphate and concentrated by evaporation in vacuo. 25.2 g (99% of theory) of bright yellow crystals were obtained, R_f = 0.45 (El D).

ESI-MS: $(M+H)^+$ = 236;
$(M-H)^-$ = 234;
$(M+Na)^+$ = 258

Example A32

Ethyl 4-methyl-1-(phenylmethyl)-2-piperazinecarboxylate

A solution of 2.2 ml (35.029 mmol) of iodomethane in 50 ml THF was added dropwise at room temperature to a mixture of 15.12 g (31.739 mmol) of ethyl 1-(phenylmethyl)-2-piperazinecarboxylate -bis-(trifluoroacetate), 20 ml DIEA and 250 ml THF and stirred for a further 4 hours at room temperature. The mixture was filtered, the residue was evaporated down in vacuo and chromatographed on a silica gel column using El II as eluant. After the appropriate fractions had been worked up in the usual way, 2.43 g (29% of theory) of a colourless oil were obtained, which was used in the next steps without further purification.

The following compounds of general formula N-B-C were prepared

analogously:

N	B	C	Remarks	% yield	EI	R_f	MS	mp. [°C]
ethyl 4-(1,1-dimethylethoxycarbonyl)-1-methyl-2-piperazinecarboxylate			from ethyl 4-(1,1-dimethylethoxy-carbonyl)-2-piperazinecarboxylate, CH_3I and DIEA in THF	79	AcOEt	0.58	ESI: $(M+H)^+$ = 273	colour-less oil
ethyl 4-(1,1-dimethylethoxycarbonyl)-1-(phenylmethyl)-2-piperazinecarboxylate			from ethyl 4-(1,1-dimethylethoxy-carbonyl)-2-piperazinecarboxylate, $PhCH_2Br$ and DIEA in THF	90	NN	0.51	ESI: $(M+H)^+$ = 349	

Example A33

Ethyl 4-(1,1-dimethylethoxycarbonyl)-2-piperazinecarboxylate

22.0 g (0.101 mol) di-*tert.*-butyl pyrocarbonate were added dropwise to a solution of 17.07 g (0.108 mol) ethyl 2-piperazinecarboxylate in 400 ml of ethanol while cooling with ice and the mixture was stirred for a further 3 hours while cooling externally with ice. The solvent was distilled off, lastly in vacuo, and the residue remaining was distributed between water and ethyl acetate. The organic phase was dried over sodium sulphate and evaporated down in vacuo, the residue was purified by column chromatography on silica gel using ethyl acetate/ethanol 95/5 v/v as eluant.
Yield: 11.798 g (42% of theory) of a colourless solid.

Example A34

Ethyl 1,4-bis-(phenylmethyl)-2-piperazinecarboxylate

A solution of 56.441 g (217.141 mmol) of ethyl 2,3-dibromopropanoate in 55 ml of toluene was added dropwise to a solution, heated to 40 °C, of 52.190 g (217.141 mmol) of *N,N'*-dibenzylethylenediamine and 60 ml triethylamine in 165 ml of toluene, with vigorous stirring, and stirred for a further 3 hours at a bath temperature of 80°C. The mixture was left to cool, filtered, the filtrates were washed twice with 50 ml of water, then once with 100 ml of saturated saline solution, dried over sodium sulphate and evaporated down in vacuo. 73.4 g (100% of theory) of a colourless viscous oil were obtained, R_f 0.79 (El MM), which was used without further purification in the following step.
ESI-MS: $(M+H)^+ = 339$

B. Preparation of the final compounds

Example 1

Ethyl 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-1-piperazineacetate (Ser. no. 1)

The mixture of 954.048 mg (1.6 mmol) 3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosine, 955.898 mg (1.6 mmol) ethyl 4-(4-piperidinyl)-1-piperazin-acetate, 802.75 mg (2.5 mmol) TBTU, 216.208 mg (1.6 mmol) HOBt, 2.4 ml (14.02 mmol) DIEA and 8 ml THF-DMF-mixture (5/3 v/v) was stirred overnight at ambient temperature. The reaction mixture was stirred into 50 ml of saturated aqueous sodium hydrogen carbonate solution, the precipitated solid was purified by column chromatography on silica gel using El G as eluant. After the eluates had been worked up in the usual way 283 mg (21% of theory) of a colourless amorphous product were obtained, R_f 0.39 (El G).

IR (KBr): 3405(NH, OH); 1731 (C=O) cm^{-1}

ESI: $(M-H)^-$ = 830/832/834(Br_2);
$(M+Na)^+$ = 854/856/858(Br_2)

The following compounds of general formula N-B-C were prepared analogously:

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
3	N1	B1	C3	from N1-CO-B1-OH, H-C3, TBTU, HOBt and DIEA in THF	71	G	0.34	ESI: $(M-H)^-$ = 858/860/862 (Br_2); $(M+Na)^+$ = 882/884/886 (Br_2)	1740 (C=O)	colourless amorphous substance
5	N1	B1	C5	from N1-CO-B1-OH, H-C5 * 2 CF_3CO_2H, TBTU, HOBt and DIEA in THF	56	G	0.36	ESI: $(M-H)^-$ = 815/817/819 (Br_2); $(M+Na)^+$ = 839/841/843 (Br_2)		colourless amorphous substance
7	N1	B1	C7	from N1-CO-B1-OH, H-C7, TBTU, HOBt and DIEA in THF	53	G	0.37	ESI: $(M-H)^-$ = 815/817/819 (Br_2); $(M+H)^+$ = 817/819/821 (Br2);$(M+Na)^+$ = 839/841/843 (Br_2)	3421 broad (NH, OH); 1726 (C=O)	colourless amorphous substance
9	N1	B1	C9	from N1-CO-B1-OH, H-C9, TBTU, HOBt and DIEA in THF	46	G	0.40	ESI: $(M-H)^-$ = 815/817/819 (Br_2); $(M+H)^+$ = 817/819/821 (Br_2)		colourless amorphous substance
11	N1	B1	C11	from N1-CO-B1-OH, H-C11, TBTU, HOBt and DIEA in THF	51	G	0.32	ESI: $(M-H)^-$ = 830/832/834 (Br_2)	3317 broad (NH, OH); 1738 (C=O)	colourless amorphous substance
12	N2	B2	C5	from N2-CO-B2-OH, H-C5, TBTU, HOBt and DIEA in THF	96	G	0.61	ESI: (M+H)+ = 830/832/834; $(M+HCO_2)^-$ = 874/876/878 (Br_2)	3377 broad (NH, NH_2); 1734 (C=O)	colourless amorphous substance

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
14	N2	B2	C11	from N2-CO-B2-OH, H-C11, TBTU, HOBt and DIEA in THF	82	G	0.57	ESI: $(M+HCO_2)^-$ = 889/891/893 (Br_2)	3446 broad (NH, NH_2); 1734 (C=O)	colourless amorphous substance
15	N1	B3	C1	from N1-CO-B3-OH, H-C1 * 3 CF_3CO_2H, TBTU, HOBt and DIEA in DMF (Chemspeed)	26			ESI: $(M+H)^+$ = 766/768 (Br)	1669 (C=O)	
16	N1	B4	C1	from N1-CO-B4-OH, H-C1 * 3 CF_3CO_2H, TBTU, HOBt and DIEA in DMF (Chemspeed)	24			ESI: $(M+H)^+$ = 742/744/746 (Cl_2)		
17	N1	B5	C1	from N1-CO-B5-OH, H-C1 * 3 CF_3CO_2H, TBTU, HOBt and DIEA in DMF (Chemspeed)	37			ESI: $(M+H)^+$ = 816/818/820 (Br_2)		
18	N1	B6	C1	from N1-CO-B6-OH, H-C1 * 3 CF_3CO_2H, TBTU, HOBt and DIEA in DMF (Chemspeed)	26			ESI: $(M+Na)^+$ = 788/790 (Br)		
19	N1	B7	C1	from N1-CO-B7-OH, H-C1 * 3 CF_3CO_2H, TBTU, HOBt and DIEA in DMF (Chemspeed)	18			ESI: $(M+Na)^+$ = 852/854/856 (Br_2)		
20	N1	B8	C1	from N1-CO-B8-OH, H-C1 * 3 CF_3CO_2H, TBTU, HOBt and DIEA in DMF (Chemspeed)	13			ESI: $(M+H)^+$ = 708/710 (Cl)		

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
21	N1	B3	C11	from N1-CO-B3-OH, H-C11, TBTU, HOBt and DIEA in DMF (Chemspeed)	26			ESI: $(M+Na)^+$ = 788/790 (Br)		
29	N1	B9	C12	from N1-CO-B9-OH, H-C12, TBTU, HOBt and DIEA in DMF (Chemspeed)	40			ESI: $(M+H)^+$ = 724		
30	N1	B10	C5	from N1-CO-B10-OH, H-C5, TBTU, HOBt and DIEA in DMF (Chemspeed)	66	G	0.35	ESI: $(M+H)^+$ = 661	1662 (C=O)	colourless amorphous substance
31	N1	B10	C1	from N1-CO-B10-OH, H-C1, TBTU, HOBt and DIEA in DMF (Chemspeed)	22			ESI: $(M+H)^+$ = 676	1734, 1660 (C=O)	colourless amorphous substance
32	N1	B21	C1	from N1-CO-B21-OH, H-C1, TBTU and NEt_3 in THF/DMF (10/1 v/v)	13			ESI: $(M-H)^-$ = 827/829/831 (Br_2); $(M+H)^+$ = 829/831/833 (Br_2)	1670 (C=O)	colourless amorphous substance
33	N1	B2	C14	from N1-CO-B2-OH, H-C14, TBTU and NEt_3 in THF/DMF (1/1 v/v)	33	S	0.67	ESI: $(M+H)^+$ = 788/790/792 (Br_2); $(M+Na)^+$ = 810/812/814 (Br_2)	3435, 3373 (NH, NH_2); 1734, 1668 (C=O)	184.6
34	N1	B1	C14	from N1-CO-B1-OH, H-C14, TBTU and NEt_3 in THF/DMF (1/1 v/v)	6	S	0.67	ESI: $(M-H)^-$ = 787/789/791 (Br_2); $(M+H)^+$ = 789/791/793 (Br_2)	1653 (C=O)	141.9
37	N1	B2	C16	from N1-CO-B2-OH, H-C16, TBTU and NEt_3 in THF/DMF (1/1 v/v)	53	S	0.67	ESI: $(M+H)^+$ = 788/790/792 (Br_2)	3437 (NH, NH_2); 1653 (C=O)	colourless crystals

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
38	N1	B1	C16	from N1-CO-B1-OH, H-C16, TBTU and NEt_3 in THF/DMF (1/1 v/v)	32	S	0.67	ESI: $(M+H)^+$ = 789/791/793 (Br_2)	3321 (NH, OH); 1662 (C=O)	colourless crystals
41	N1	B2	C18	from N1-CO-B2-OH, H-C18 * AcOH, TBTU and NEt_3 in THF/DMF (1/1 v/v)	26	G	0.35	ESI: $(M+H)^+$ = 802/804/806 (Br_2)		colourless crystals
42	N1	B1	C18	from N1-CO-B1-OH, H-C18 * AcOH, TBTU and NEt_3 in THF/DMF (1/1 v/v)	35	G	0.47	ESI: $(M+H)^+$ = 803/805/807 (Br_2)		colourless crystals
43	N1	B2	C19	from N1-CO-B2-OH, H-C19, TBTU and NEt_3 in THF/DMF (1/1 v/v)	52	Q	0.73	ESI: $(M+H)^+$ = 802/804/806 (Br_2); $(M+Na)^+$ = 824/826/828 (Br_2)		colourless crystals
44	N1	B1	C19	from N1-CO-B1-OH, H-C19, TBTU and NEt_3 in THF/DMF (1/1 v/v)	63	Q	0.72	ESI: $(M+H)^+$ = 803/805/807 (Br_2)		colourless crystals
49	N1	B1	C22	from N1-CO-B1-OH, H-C22, TBTU and NEt_3 in THF/DMF (1/1 v/v)	49	G	0.44	ESI: $(M-H)^-$ = 801/803/805 (Br_2)		colourless crystals
50	N1	B2	C22	from N1-CO-B2-OH, H-C22, TBTU and NEt_3 in THF/DMF (1/1 v/v)	70	G	0.65	ESI: $(M+H)^+$ = 802/804/806 (Br_2)		colourless crystals
55	N1	B1	C26	from N1-CO-B1-OH, H-C26, TBTU, HOBt and DIEA in THF	52	D	0.55	ESI: $(M-H)^-$ = 809/811/813 (Br_2)		colourless crystals
56	N1	B1	C27	from N1-CO-B1-OH, H-C27 * 2 HBr, TBTU, HOBt and DIEA in THF	54	D	0.56	ESI: $(M-H)^-$ = 809/811/813 (Br_2)		colourless crystals

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
57	N1	B1	C28	from N1-CO-B1-OH, H-C28, TBTU, HOBt and DIEA in THF	33	D	0.56	ESI: $(M-H)^-$ = 794/796/798 (Br_2)		colourless crystals
58	N1	B1	C29	from N1-CO-B1-OH, H-C29, TBTU, HOBt and DIEA in THF	32	D	0.57	ESI: $(M-H)^-$ = 822/824/826 (Br_2)		colourless crystals
59	N1	B1	C30	from N1-CO-B1-OH, H-C30, TBTU, HOBt and DIEA in THF	25	D	0.68	ESI: $(M-H)^-$ = 836/838/840 (Br_2); $(M+Na)^+$ = 860/862/864 (Br_2)	1716, 1662 (C=O)	colourless crystals
60	N1	B1	C31	from N1-CO-B1-OH, H-C31 * 2 HCl, TBTU, HOBt and DIEA in THF	55	D	0.59	ESI: $(M-H)^-$ = 863/865/867 (Br_2)		colourless crystals
61	N1	B1	C32	from N1-CO-B1-OH, H-C32 * HCl, TBTU, HOBt and DIEA in THF	45	D	0.59	ESI: $(M-H)^-$ = 794/796/798 (Br_2); $(M+Na)^+$ = 818/820/822 (Br_2)		colourless crystals
62	N2	B2	C26	from N2-CO-B2-OH, H-C26, TBTU, HOBt and DIEA in THF	62	D	0.81	ESI: $(M-H)^-$ = 822/824/826 (Br_2); $(M+Na)^+$ = 846/848/850 (Br_2)		colourless crystals
63	N2	B2	C27	from N2-CO-B2-OH, H-C27 * 2 HBr, TBTU, HOBt and DIEA in THF	65	D	0.79	ESI: $(M+Na)^+$ = 846/848/850 (Br_2)		colourless crystals
64	N2	B2	C28	from N2-CO-B2-OH, H-C28, TBTU, HOBt and DIEA in THF	38	D	0.81	ESI: $(M-H)^-$ = 807/809/811 (Br_2)		colourless crystals
65	N2	B2	C30	from N2-CO-B2-OH, H-C30, TBTU, HOBt and DIEA in THF	54	D	0.87	ESI: $(M+Na)^+$ = 873/875/877 (Br_2)		colourless crystals
66	N2	B2	C31	from N2-CO-B2-OH, H-C31 * 2 HCl, TBTU, HOBt and DIEA in THF	50	D	0.85	ESI: $(M+Na)^+$ = 900/902/904 (Br_2)		colourless crystals

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
67	N2	B2	C32	from N2-CO-B2-OH, H-C32 * HCl, TBTU, HOBt and DIEA in THF	52	D	0.88	ESI: $(M-H)^-$ = 807/809/811 (Br_2); $(M+Na)^+$ = 831/833/835 (Br_2)	1723 (C=O)	colourless crystals
83	N1	B1	C40	from N1-CO-B1-OH, H-C40, TBTU, HOBt and DIEA in THF	17	D	0.50	ESI: $(M-H)^-$ = 802/804/806 (Br_2); $(M+Na)^+$ = 826/828/830 (Br_2)		colourless crystals
84	N1	B1	C41	from N1-CO-B1-OH, H-C41 * HCl, TBTU, HOBt and DIEA in THF	82	D	0.41	ESI: $(M-H)^-$ = 802/804/806 (Br_2)		
87	N1	B2	C41	from N1-CO-B2-OH, H-C41 * HCl, TBTU, HOBt and DIEA in THF	75	D	0.62	ESI: $(M-H)^-$ = 801/803/805 (Br_2)		
88	N1	B2	C40	from N1-CO-B2-OH, H-C40, TBTU, HOBt and DIEA in THF	62	D	0.52	ESI: $(M+Na)^+$ = 825/827/829 (Br_2)		
93	N1	B2	C12	from N1-CO-B2-OH, H-C12, TBTU, HOBt and DIEA in THF	55	D	0.47	ESI: $(M-H)^-$ = 857/859/861 (Br_2); $(M+H)^+$ = 859/861/863 (Br_2); $(M+Na)^+$ = 881/883/885 (Br_2)	1665 (C=O)	colourless crystals
94	N2	B2	C12	from N2-CO-B2-OH, H-C12, TBTU, HOBt and DIEA in THF	65	D	0.49	ESI: $(M-H)^-$ = 871/873/875 (Br_2); $(M+Na)^+$ = 895/897/899 (Br_2)		colourless crystals
95	N1	B2	C1	from N1-CO-B2-OH, H-C1, TBTU, HOBt and DIEA in THF	57	D	0.68	ESI: $(M+H)^+$ = 831/833/835 (Br_2)	1665 (C=O)	colourless crystals
96	N2	B2	C1	from N2-CO-B2-OH, H-C1, TBTU, HOBt and DIEA in THF	58	D	0.72	ESI: $(M-H)^-$ = 843/845/847 (Br_2); $(M+H)^+$ = 845/847/849 (Br_2)	1658 (C=O)	colourless crystals

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
119	N1	B30	C1	from N1-CO-B30-OH, H-C1, TBTU, HOBt and DIEA in THF	50			ESI: $(M+H)^+$ = 815/817/819 (Br_2)		colourless crystals
122	N1	B7	C14	from N1-CO-B7-OH, H-C14, TBTU and NEt_3 in DMF	26	II	0.44	ESI: $(M+H)^+$ = 787/789/791 (Br_2)		colourless amorphous substance
123	N1	B8	C14	from N1-CO-B8-OH, H-C14, TBTU and NEt_3 in DMF	28	C	0.68	ESI: $(M+H)^+$ = 665/667 (Cl)		highly viscous oil
124	N1	B7	C16	from N1-CO-B7-OH, H-C16, TBTU and NEt_3 in DMF	20	C	0.80	ESI: $(M+H)^+$ = 787/789/791 (Br_2)		highly viscous oil
125	N1	B8	C16	from N1-CO-B8-OH, H-C16, TBTU and NEt_3 in DMF	11	II	0.58	ESI: $(M+H)^+$ = 665/667 (Cl)		colourless amorphous substance
128	N1	B32	C45	from N1-CO-B32-OH, H-C45, TBTU, HOBt and NEt_3 in DMF	4	C	0.45	ESI: $(M+H)^+$ = 703		colourless solid substance
129	N1	B30	C45	from N1-CO-B30-OH, H-C45, TBTU and DIEA in THF	19	C	0.72	ESI: $(M+H)^+$ = 815/817/819 (Br_2)		colourless solid substance
130	N1	B30	C44	from N1-CO-B30-OH, H-C44, TBTU and DIEA in THF	18	C	0.81	ESI: $(M+H)^+$ = 815/817/819 (Br_2)		colourless solid substance
131	N1	B21	C45	from N1-CO-B21-OH, H-C45, TBTU and DIEA in THF	14	C	0.67	ESI: $(M+H)^+$ = 829/831/833 (Br_2)		colourless solid substance
132	N1	B21	C44	from N1-CO-B21-OH, H-C44, TBTU and DIEA in THF	24	C	0.48	ESI: $(M+H)^+$ = 829/831/833 (Br_2)		colourless solid substance
133	N1	B30	C46	from N1-CO-B30-OH, H-C46, TBTU and DIEA in THF	16	C	0.55	ESI: $(M+H)^+$ = 815/817/819 (Br_2)		colourless solid substance

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
138	N1	B21	C46	from N1-CO-B21-OH, H-C46, PyBroP and DIEA in THF	26	Q	0.65	ESI: $(M+H)^+$ = 829/831/833 (Br_2)		colourless solid substance
140	N1	B31	C44	from N1-CO-B31-OH, H-C44, PyBroP and DIEA in THF	22	Q	0.57	ESI: $(M+H)^+$ = 830/832/834 (Br_2)		colourless solid substance
141	N1	B31	C46	from N1-CO-B31-OH, H-C46, PyBroP and DIEA in THF	15	Q	0.47	ESI: $(M+H)^+$ = 830/832/834 (Br_2)		colourless solid substance
142	N1	B31	C45	from N1-CO-B31-OH, H-C45, PyBroP and DIEA in THF	11	Q	0.59	ESI: $(M+H)^+$ = 830/832/834 (Br_2)		colourless solid substance
148	N1	B32	C44	from N1-CO-B32-OH, H-C44, HATU and DIEA in THF	24	Q	0.50	ESI: $(M+H)^+$ = 703	1736, 1664, 1637 (C=O)	colourless solid substance
149	N1	B32	C46	from N1-CO-B32-OH, H-C46, HATU and DIEA in THF	3	Q	0.50	M^+ = 702		colourless solid substance
151	N1	B25	C45	from N1-CO-B25-OH, H-C45, TBTU and DIEA in THF	10	G	0.38	ESI: $(M+H)^+$ = 805/807/809 (Cl_2)		colourless solid substance
152	N1	B30	C50	from N1-CO-B30-OH, H-C50, TBTU and DIEA in THF	21	G	0.28	ESI: $(M+H)^+$ = 815/817/819 (Br_2)		colourless solid substance
153	N1	B21	C50	from N1-CO-B21-OH, H-C50, TBTU and DIEA in THF	34	G	0.36	ESI: $(M+H)^+$ = 829/831/833 (Br_2)	3439 (NH); 1738, 1666, 1639 (C=O)	colourless solid substance
154	N1	B32	C50	from N1-CO-B32-OH, H-C50, TBTU and DIEA in THF	46	G	0.35	ESI: $(M+H)^+$ = 703	1736, 1660, 1628 (C=O)	colourless solid substance

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
155	N1	B31	C50	from N1-CO-B31-OH, H-C50, TBTU and DIEA in THF	30	Q	0.66	ESI: $(M+H)^+$ = 830/832/834 (Br_2)	3458 (NH, NH_2); 1734 (C=O)	colourless solid substance
156	N1	B25	C50	from N1-CO-B25-OH, H-C50, TBTU and DIEA in THF	29	Q	0.68	ESI: $(M+H)^+$ = 806/807/809/811 (Br_2, Cl)	3439 (NH); 1639 (C=O)	colourless solid substance
162	N1	B5	C45	from N1-CO-B5-OH, H-C45, TBTU and DIEA in THF/DMF (3/1 v/v)	22	C	0.69	ESI: $(M+H)^+$ = 816/818/820 (Br_2)		colourless solid substance
164	N1	B33	C5	from N1-CO-B33-OH, H-C5, TBTU and DIEA in THF	70	C	0.79	ESI: $(M+H)^+$ = 801/803/805 (Br_2)		colourless solid substance
166	N1	B7	C45	from N1-CO-B7-OH, H-C45, TBTU and DIEA in THF/DMF	25	C	0.69	ESI: $(M+H)^+$ = 830/832/834 (Br_2)	1738, 1660 (C=O)	colourless solid substance
167	N1	B7	C50	from N1-CO-B7-OH, H-C50, TBTU and DIEA in THF/DMF	41	C	0.71	ESI: $(M+H)^+$ = 830/832/834 (Br_2)	1736, 1662 (C=O)	colourless solid substance

Example 2

4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-1-piperazine-acetic acid (Ser. no. 2)

0.5 ml of 1M aqueous sodium hydroxide solution was added to a solution of 85.0 mg (0.102 mmol) of ethyl 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-1-piperazine-acetate in 3.5 ml of methanol at room temperature and the mixture was stirred for 1 hour at a reaction temperature of 40°C. The solvent was eliminated in vacuo and then neutralised while cooling externally with ice by

the addition of 0.5 ml 1M hydrochloric acid. The mixture was left to stand for 2 hours at room temperature before the precipitated crystals were collected. The mother liquor was evaporated down again, the residue was digested with a few drops of water to eliminate inorganic salts, left to stand for 2 hours and then filtered. The combined solids were dried in vacuo, triturated with diethyl ether and yielded 80.0 mg (97% of theory) of colourless crystals.

ESI-MS: $(M+Na)^+$ = 826/828/830 (Br_2)

$(M-H)^-$ = 802/804/806 (Br_2)

The following compounds of general formula N-B-C were prepared analogously:

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
4	N1	B1	C4	from N1-CO-B1-C3 with aq. 1M NaOH, then aq. 1M HCl	88	G	0.02	ESI: $(M-H)^-$ = 802/804/806 (Br_2); $(M+Na)^+$ = 826/828/830 (Br_2)		colourless crystals
6	N1	B1	C6	from N1-CO-B1-C5 with aq. 1M NaOH, then aq. 1M HCl	88	G	0.02	ESI: $(M-H)^-$ = 801/803/805 (Br_2); $(M+H)^+$ = 803/805/807 (Br2); $(M+Na)^+$ = 825/827/829 (Br_2)	3420 (NH, OH), 1734, 1653 (C=O)	colourless crystals
8	N1	B1	C8	from N1-CO-B1-C7 with aq. 1M NaOH, then aq. 1M HCl	96	G	0.02	ESI: $(M-H)^-$ = 787/789/791 (Br_2); $(M+Na)^+$ = 811/813/815 (Br_2)	3420 (NH, OH), 1709, 1653 (C=O)	colourless crystals
10	N1	B1	C10	from N1-CO-B1-C9 with aq. 1M NaOH, then aq. 1M HCl	72	G	0.03	ESI: $(M-H)^-$ = 787/789/791 (Br_2); $(M+Na)^+$ = 811/813/815 (Br_2)	3413 (NH, OH), 1707, 1653 (C=O)	colourless crystals

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
13	N2	B2	C6	from N2-CO-B2-C5 with aq. 1M NaOH, then aq. 1M HCl	78	G	0.04	ESI: $(M-H)^-$ = 814/816/818 (Br_2); $(M+H)^+$ = 816/818/820 (Br2); $(M+HCO_2)^-$ = 859/861/863 (Br_2)	3431 (NH, NH_2); 1653 (C=O)	colourless crystals
22	N1	B3	C2	from N1-CO-B3-C1 with aq. 1M NaOH, then aq. 1M HCl	97			ESI: $(M+H)^+$ = 738/740 (Br)	3425 (NH), 1659, 1632 (C=O)	colourless crystals
23	N1	B4	C2	from N1-CO-B4-C1 with aq. 1M NaOH, then aq. 1M HCl	99			ESI: $(M+Cl)^-$ = 748/750/752/754 (Cl_2); $(M+Na)^+$ = 736/738/740 (Cl_2)	3419 (NH), 1655, 1628 (C=O)	colourless crystals
24	N1	B5	C2	from N1-CO-B5-C1 with aq. 1M NaOH, then aq. 1M HCl	98			ESI: $(M+Cl)^-$ = 822/824/826/828 (Br_2); $(M+Na)^+$ = 810/812/814 (Br_2)	3419 (NH), 1655, 1635 (C=O)	colourless crystals
25	N1	B6	C2	from N1-CO-B6-C1 with aq. 1M NaOH, then aq. 1M HCl	98			ESI: $(M+Cl)^-$ = 772/774/776 (Br); $(M+Na)^+$ = 760/762 (Br)	3427 (NH), 1630 (C=O)	colourless crystals
26	N1	B7	C2	from N1-CO-B7-C1 with aq. 1M NaOH, then aq. 1M HCl	99			ESI: $(M+Cl)^-$ = 836/838/840/842 (Br_2); $(M+Na)^+$ = 824/826/828 (Br_2)	3419 (NH), 1655, 1635 (C=O)	colourless crystals
27	N1	B8	C2	from N1-CO-B8-C1 with aq. 1M NaOH, then aq. 1M HCl	89			ESI: $(M+Cl)^-$ = 714/716/718 (Cl); $(M+Na)^+$ = 702/704 (Cl)	3419 (NH), 1655, 1635 (C=O)	colourless crystals
28	N1	B3	C4	from N1-CO-B3-C11 with aq. 1M NaOH, then aq. 1M HCl	97			ESI: $(M+Cl)^-$ = 772/774/776 (Br); $(M+Na)^+$ = 760/762 (Br)	3416 (NH), 1655, 1635 (C=O)	colourless crystals

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
35	N1	B2	C15	from N1-CO-B2-C14 with aq. 1M LiOH, then aq. 1M HCl	78	T	0.46	ESI:$(M+Na)^+$ = 796/798/800 (Br_2)	3339 (NH, NH_2); 1653 (C=O)	colourless crystals
36	N1	B1	C15	from N1-CO-B1-C14 with aq. 1M LiOH, then aq. 1M HCl	78	T	0.42	ESI: $(M-H)^-$ = 773/775/779 (Br_2); $(M+H)^+$ = 775/777/779 (Br_2); $(M+Na)^+$ = 797/799/801 (Br_2)		colourless crystals
39	N1	B2	C17	from N1-CO-B2-C16 with aq. 1M LiOH, then aq. 1M HCl	76	T	0.46	ESI: $(M-H)^-$ = 772/774/776 (Br_2); $(M+Na)^+$ = 796/798/800 (Br_2)	3429 (NH, NH_2); 1653 (C=O)	colourless crystals
40	N1	B1	C17	from N1-CO-B1-C16 with aq. 1M LiOH, then aq. 1M HCl	70	T	0.42	ESI: $(M-H)^-$ = 773/775/777 (Br_2); $(M+Na)^+$ = 797/799/801 (Br_2)	3420 (NH, OH); 1653 (C=O)	colourless crystals
45	N1	B2	C20	from N1-CO-B2-C18 with aq. 1M LiOH, then aq. 1M HCl	96			ESI: $(M-H)^-$ = 786/788/790 (Br_2)		colourless crystals
46	N1	B1	C20	from N1-CO-B1-C18 with aq. 1M LiOH, then aq. 1M HCl	97			ESI: $(M-H)^-$ = 787/789/791 (Br_2)		colourless crystals
47	N1	B1	C21	from N1-CO-B1-C19 with aq. 1M LiOH, then aq. 1M HCl	86			ESI: $(M-H)^-$ = 787/789/791 (Br_2)		colourless crystals
48	N1	B2	C21	from N1-CO-B2-C19 with aq. 1M LiOH, then aq. 1M HCl	2			ESI: $(M-H)^-$ = 786/788/790 (Br_2); $(M+Na)^+$ = 810/812/814 (Br_2)		colourless crystals

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
51	N1	B1	C23	from N1-CO-B1-C22 with aq. 1M LiOH, then aq. 1M HCl	12			ESI: $(M-H)^-$ = 787/789/791 (Br_2)		colourless amorph-ous substance
52	N1	B2	C23	from N1-CO-B2-C22 with aq. 1M LiOH, then aq. 1M HCl	14			ESI: $(M+H)^+$ = 788/790/792 (Br_2)		colourless amorph-ous substance
53	N1	B10	C6	from N1-CO-B10-C5 with aq. 1M LiOH, then aq. citric acid	36			ESI: $(M+H)^+$ = 647		colourless amorph-ous substance
54	N1	B10	C2	from N1-CO-B10-C1 with aq. 1M LiOH, then aq. citric acid	21			ESI: $(M+H)^+$ = 648	1711, 1639 (C=O)	colourless crystals
68	N1	B1	C33	from N1-CO-B1-C26 with aq. 1M LiOH, then aq. 1M HCl	77	I	0.51	ESI: $(M-H)^-$ = 781/783/785 (Br_2)	1655 (C=O)	colourless crystals
69	N1	B1	C34	from N1-CO-B1-C27 with aq. 1M LiOH, then aq. 1M HCl	75	I	0.50	ESI: $(M-H)^-$ = 781/783/785 (Br_2); $(M+Na)^+$ = 805/807/809 (Br_2)	1637 (C=O)	colourless crystals
70	N1	B1	C35	from N1-CO-B1-C28 with aq. 1M LiOH, then aq. 1M HCl	82	I	0.52	ESI: $(M-H)^-$ = 780/782/784 (Br_2); $(M+Na)^+$ = 804/806/808 (Br_2)		colourless crystals
71	N1	B1	C36	from N1-CO-B1-C29 with aq. 1M LiOH, then aq. 1M HCl	76	I	0.54	ESI: $(M-H)^-$ = 794/796/798 (Br_2); $(M+Na)^+$ = 818/820/822 (Br_2)	1658 (C=O)	colourless crystals
72	N1	B1	C37	from N1-CO-B1-C30 with aq. 1M LiOH, then aq. 1M HCl	75	I	0.53	ESI: $(M-H)^-$ = 808/810/812 (Br_2); $(M+Na)^+$ = 832/834/836 (Br_2)	1707, 1659 (C=O)	colourless crystals

Ser. no.	N	B	C	Remarks	% yield	El	R_f	MS	IR [cm^{-1}]	mp. [°C]
73	N1	B1	C38	from N1-CO-B1-C31 with aq. 1M LiOH, then aq. 1M HCl	73	I	0.47	ESI: $(M-H)^-$ = 849/851/853 (Br_2); $(M+Na)^+$ = 873/875/877 (Br_2)		colourless crystals
74	N1	B1	C39	from N1-CO-B1-C32 with aq. 1M LiOH, then aq. 1M HCl	68	I	0.49	ESI: $(M-H)^-$ = 780/782/784 (Br_2)	1711, 1657 (C=O)	colourless crystals
75	N2	B2	C33	from N2-CO-B2-C26 with aq. 1M LiOH, then aq. 1M HCl	82	I	0.55	ESI: $(M-H)^-$ = 794/796/798 (Br_2); $(M+Na)^+$ = 818/820/822 (Br_2)		colourless crystals
76	N2	B2	C34	from N2-CO-B2-C27 with aq. 1M LiOH, then aq. 1M HCl	76	I	0.54	ESI: $(M-H)^-$ = 794/796/798 (Br_2); $(M+Na)^+$ = 818/820/822 (Br_2)	1709, 1637 (C=O)	colourless crystals
77	N2	B2	C35	from N2-CO-B2-C28 with aq. 1M LiOH, then aq. 1M HCl	76	I	0.54	ESI: $(M-H)^-$ = 793/795/797 (Br_2); $(M+Na)^+$ = 817/819/821 (Br_2)	1657 (C=O)	colourless crystals
78	N2	B2	C37	from N2-CO-B2-C30 with aq. 1M LiOH, then aq. 1M HCl	86	I	0.56	ESI: $(M-H)^-$ = 821/823/825 (Br_2); $(M+Na)^+$ = 845/847/849 (Br_2)		colourless crystals
79	N2	B2	C38	from N2-CO-B2-C31 with aq. 1M LiOH, then aq. 1M HCl	77	I	0.56	ESI: $(M-H)^-$ = 862/864/866 (Br_2); $(M+Na)^+$ = 886/888/890 (Br_2)		colourless crystals
80	N2	B2	C39	from N2-CO-B2-C32 with aq. 1M LiOH, then aq. 1M HCl	71	I	0.57	ESI: $(M-H)^-$ = 793/795/797 (Br_2)	1711 (C=O)	colourless crystals
82	N2	B11	C2	from N2-CO-B11-C1 with aq. 0.1M LiOH, then aq. 0.1M HCl	83			ESI: $(M+H)^+$ = 696		colourless amorph-ous substance

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
85	N1	B1	C42	from N1-CO-B1-C40 with aq. 0.1M LiOH, then aq. 0.1M HCl	97	O	0.12	ESI: $(M-H)^-$ = 788/790/792 (Br_2)		colourless crystals
86	N1	B1	C43	from N1-CO-B1-C41 with aq. 0.1M LiOH, then aq. 0.1M HCl	82	O	0.16	ESI: $(M-H)^-$ = 788/790/792 (Br_2)		colourless crystals
89	N1	B2	C43	from N1-CO-B2-C41 with aq. 0.1M LiOH, then aq. 0.1M HCl	76	D	0.15	ESI: $(M-H)^-$ = 787/789/791 (Br_2)		colourless crystals
90	N1	B2	C42	from N1-CO-B2-C40 with aq. 0.1M LiOH, then aq. 0.1M HCl	86	D	0.16	ESI: $(M-H)^-$ = 787/789/791 (Br_2)		colourless crystals
91	N1	B2	C4	from N1-CO-B2-C11 with aq. 0.1M LiOH, then aq. 0.1M HCl	86	M	0.24	ESI: $(M-H)^-$ = 801/803/805 (Br_2); $(M+H)^+$ = 803/805/807 (Br_2)	1653 (C=O)	colourless crystals
92	N2	B2	C4	from N2-CO-B2-C11 with aq. 0.1M LiOH, then aq. 0.1M HCl	69	M	0.31	ESI: $(M-H)^-$ = 815/817/819 (Br_2); $(M+Na)^+$ = 839/841/843 (Br_2)		colourless crystals
97	N1	B2	C2	from N1-CO-B2-C1 with aq. 1M LiOH, then aq. 1M HCl	61	D	0.06	ESI: $(M-H)^-$ = 801803/805 (Br_2); $(M+Na)^+$ = 825/827/829 (Br_2)	1653 (C=O)	colourless crystals
98	N2	B2	C2	from N2-CO-B2-C1 with aq. 1M LiOH, then aq. 1M HCl	73	D	0.05	ESI: $(M-H)^-$ = 815/817/819 (Br_2); $(M+H)^+$ = 817/819/821 (Br_2); $(M+Na)^+$ = 839/841/843 (Br_2)		colourless crystals

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
120	N1	B30	C2	from N1-CO-B30-C1 with aq. 1M NaOH, then aq. 1M HCl	40			ESI: $(M-H)^-$ = 785/787/789 (Br_2); $(M+H)^+$ = 787/789/791 (Br_2)		colourless amorph-ous substance
121	N1	B30	C4	from N1-CO-B30-C11 with aq. 1M NaOH, then aq. 1M HCl	48			ESI: $(M-H)^-$ = 785/787/789 (Br_2); $(M+H)^+$ = 787/789/791 (Br_2)		colourless amorph-ous substance
126	N1	B7	C15	from N1-CO-B7-C14 with aq. 1M LiOH, then aq. 1M HCl	77	C	0.00	ESI: $(M+H)^+$ = 773/775/777 (Br_2)		colourless solid substance
127	N1	B8	C15	from N1-CO-B8-C14 with aq. 1M LiOH, then aq. 1M HCl	100	C	0.00	ESI: $(M+H)^+$ = 651/657 (Cl)		colourless solid substance
134	N1	B30	C47	from N1-CO-B30-C45 with aq. 1M LiOH, then aq. 1M HCl	68	KK	0.25	ESI: $(M+H)^+$ = 787/789/791 (Br_2)		colourless solid substance
135	N1	B30	C48	from N1-CO-B30-C44 with aq. 1M LiOH, then aq. 1M HCl	29	KK	0.14	ESI: $(M+H)^+$ = 787/789/791 (Br_2)		colourless solid substance
136	N1	B30	C49	from N1-CO-B30-C46 with aq. 1M LiOH, then aq. 1M HCl	78	KK	0.10	ESI: $(M-H)^-$ = 785/787/789 (Br_2)		colourless solid substance
137	N1	B21	C47	from N1-CO-B21-C45 with aq. 1M LiOH, then aq. 1M HCl	81	KK	0.24	ESI: $(M+H)^+$ = 801/803/805 (Br_2)		colourless solid substance
139	N1	B21	C48	from N1-CO-B21-C44 with aq. 1M LiOH, then aq. 1M HCl	51	KK	0.11	ESI: $(M+H)^+$ = 801/803/805 (Br_2)		colourless solid substance

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
143	N1	B31	C48	from N1-CO-B31-C44 with aq. 1M LiOH, then aq. 1M HCl	74	KK	0.11	ESI: $(M+H)^+$ = 802/804/806 (Br_2)		colourless solid substance
145	N1	B31	C47	from N1-CO-B31-C45 with aq. 1M LiOH, then aq. 1M HCl	72	KK	0.23	ESI: $(M+H)^+$ = 802/804/806 (Br_2)		colourless solid substance
146	N1	B31	C49	from N1-CO-B31-C46 with aq. 1M LiOH, then aq. 1M HCl	62	KK	0.07	ESI: $(M+H)^+$ = 802/804/806 (Br_2)		colourless solid substance
147	N1	B21	C49	from N1-CO-B21-C46 with aq. 1M LiOH, then aq. 1M HCl	92	KK	0.08	ESI: $(M+H)^+$ = 801/803/805 (Br_2)		colourless solid substance
150	N1	B32	C47	from N1-CO-B32-C45 with aq. 1M LiOH, then aq. 1M HCl	17	KK	0.14	ESI: $(M+H)^+$ = 675		colourless solid substance
157	N1	B21	C51	from N1-CO-B21-C50 with aq. 1M LiOH, then aq. 1M HCl	75	Q	0.35	ESI: $(M+H)^+$ = 801/803/805 (Br_2)		colourless amorph-ous substance
158	N1	B32	C51	from N1-CO-B32-C50 with aq. 1M LiOH, then aq. 1M HCl	20	KK	0.13	ESI: $(M-H)^-$ = 673; $(M+H)^+$ = 675		colourless amorph-ous substance
159	N1	B31	C51	from N1-CO-B31-C50 with aq. 1M LiOH, then aq. 1M HCl	91	OO	0.60	ESI: $(M+H)^+$ = 802/804/806 (Br_2)		colourless amorph-ous substance
160	N1	B25	C51	from N1-CO-B25-C50 with aq. 1M LiOH, then aq. 1M HCl	82	Q	0.25	ESI: $(M+H)^+$ = 777/779/781/783 ($BrCl_2$)		colourless amorph-ous substance

Ser. no.	N	B	C	Remarks	% yield	EI	R_f	MS	IR [cm^{-1}]	mp. [°C]
161	N1	B30	C51	from N1-CO-B30-C50 with aq. 1M LiOH, then aq. 1M HCl	73	Q	0.32	ESI: $(M+H)^+$ = 787/789/791 (Br_2)		colourless amorph-ous substance
163	N1	B25	C47	from N1-CO-B25-C45 with aq. 1M LiOH, then aq. 1M HCl	90	KK	0.17	ESI: $(M+H)^+$ = 777/779/781/783 ($BrCl_2$)		colourless amorph-ous substance
165	N1	B33	C6	from N1-CO-B33-C5 with aq. 1M LiOH, then aq. 1M HCl	78	KK	0.16	ESI: $(M+H)^+$ = 787/789/791 (Br_2)		colourless solid substance

Example 3

Ethyl 4-{1-[3-(1-naphthyl)-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-alanyl]-4-piperidinyl}-1-piperazineacetate (Ser. no. 81)

A tetrahydrofuran solution (20 ml) of 380.0 mg (0.84 mmol) ethyl 4-{1-[3-(1-naphthyl)-D-alanyl]-4-piperidinyl}-1-piperazineacetate was added dropwise over a period of 40 minutes to a stirred suspension of 149.356 mg (0.91 mmol) CDT in 10 ml of tetrahydrofuran cooled to -5 °C. The reaction mixture was then stirred for 1 hour at –5 °C and 1 hour at ambient temperature and combined with the suspension of 206.075 mg (0.84 mmol) 3-(4-piperidinyl)-1,3,4,5-tetrahydro-1,3-benzodiazepin-2-one in 10 ml DMF. In order to obtain a homogeneous mixture, the tetrahydrofuran was distilled off at normal pressure, another 15 ml of DMF were added and the mixture was then heated to 100 °C for 2 hours. The reaction mixture was evaporated down in vacuo, the residue was purified by column chromatography using a gradient method developed in-house using mixtures of dichloromethane, methanol and conc. ammonia on silica gel, the appropriate fractions were triturated with ether and the solid obtained (450.0 mg; 74% of theory) was suction filtered and dried.

ESI-MS: $(M+H)^+ = 724$

Example 4

(*R,S*)-4-{1-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid (Ser. no. 99)

This and the following syntheses were carried out using the Chemspeed ASW2000 synthesising robot (Chemspeed Ltd., Rheinstraße 32, CH-4302 Augst, Switzerland).

Mixture:

AGV 1: 118.862 mg (0.200 mmol) of (*R,S*)-2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-4-oxobutanoic acid in 3 ml THF;

AGV 2: 51.073 mg (0.200 mmol) of ethyl 4-(4-piperidinyl)-1-piperazineacetate in 2 ml THF;

AGV 3: 64.220 mg (0.200 mmol) of TBTU in 2 ml DMF;

AGV 4: 1.00 ml (1.00 mmol) of triethylamine;

AGV 5: 1.00 ml 4M sodium hydroxide solution;

AGV 6: 1.00 ml 4M hydrochloric acid;

AGV 7: 6 ml THF.

AGV 1 to 4 were positioned accordingly, then pipetted together by the robot and shaken for 8 hours at room temperature. The reaction mixtures were concentrated by evaporation, each combined with 7 ml of ethyl acetate, the solutions formed were each washed with 10 ml 10% aqueous potassium carbonate solution and with 6 ml of water and again freed from solvent. The residues were each dissolved in AGV 7 and after the addition of AGV 5 stirred for six hours at room temperature. The reaction mixtures were neutralised by the addition of AGV 6, then concentrated by evaporation. The residues obtained were each dissolved in 1.9 ml DMF and placed on a microtitre plate. The samples were in each case separated using an HPLC-MS apparatus

(Agilent Technologies, Agilent 1100 Series Modules and Systems for HPLC and LC/MS), the products of interest were collected under mass control. The end products were freeze-dried.

Yield: 26.0 mg (15% of theory).

ESI-MS: $(M-H)^-$ = 800/802/804 (Br_2)

$(M+H)^+$ = 802/804/806 (Br_2)

The following compounds of general formula N-B-C were prepared analogously:

Ser. no.	N	B	C	Remarks	% yield	MS
100	N1	B12	C2	coupling of N1-CO-B12-OH with H-C1 and subsequent saponification with aq. NaOH	8	ESI: $(M-H)^-$ = 803/805/807 (Br_2); $(M+H)^+$ = 805/807/809 (Br_2)
101	N5	B13	C2	coupling of N5-CO-B13-OH with H-C1 and subsequent saponification with aq. NaOH	6	ESI: $(M+H)^+$ = 682
102	N1	B14	C2	coupling of N1-CO-B14-OH with H-C1 and subsequent saponification with aq. NaOH	6	ESI: $(M+H)^+$ = 767
103	N1	B15	C2	coupling of N1-CO-B15-OH with H-C1 and subsequent saponification with aq. NaOH	6	ESI: $(M+H)^+$ = 673
104	N1	B16	C2	coupling of N1-CO-B16-OH with H-C1 and subsequent saponification with aq. NaOH	6	ESI: $(M-H)^-$ = 735/737 (Br); $(M+H)^+$ = 737/739 (Br)
105	N1	B17	C2	coupling of N1-CO-B17-OH with H-C1 and subsequent saponification with aq. NaOH	10	ESI: $(M+H)^+$ = 699
106	N1	B18	C2	coupling of N1-CO-B18-OH with H-C1 and subsequent saponification with aq. NaOH	4	ESI: $(M+H)^+$ = 689

Ser. no.	N	B	C	Remarks	% yield	MS
107	N1	B19	C2	coupling of N1-CO-B19-OH with H-C1 and subsequent saponification with aq. NaOH	4	ESI: $(M-H)^-$ = 712/714/716 (Cl_2); $(M+H)^+$ = 714/716/718 (Cl_2)
108	N1	B20	C2	coupling of N1-CO-B20-OH with H-C1 and subsequent saponification with aq. NaOH	4	ESI: $(M+H)^+$ = 767
109	N1	B21	C2	coupling of N1-CO-B21-OH with H-C1 and subsequent saponification with aq. NaOH	13	ESI: $(M-H)^-$ = 799/801/803 (Br_2); $(M+H)^+$ = 801/803/805 (Br_2)
110	N1	B22	C2	coupling of N1-CO-B22-OH with H-C1 and subsequent saponification with aq. NaOH	4	ESI: $(M+H)^+$ = 865/867/869/871 (Br_3)
111	N1	B23	C2	coupling of N1-CO-B23-OH with H-C1 and subsequent saponification with aq. NaOH	12	ESI: $(M+H)^+$ = 691
112	N1	B24	C2	coupling of N1-CO-B24-OH with H-C1 and subsequent saponification with aq. NaOH	2	ESI: $(M+H)^+$ = 699/701/703 (Cl_2)
113	N1	B25	C2	coupling of N1-CO-B25-OH with H-C1 and subsequent saponification with aq. NaOH	4	ESI: $(M+H)^+$ = 777/779/781 (Br, Cl_2)
114	N1	B26	C2	coupling of N1-CO-B26-OH with H-C1 and subsequent saponification with aq. NaOH	3	ESI: $(M+H)^+$ = 681
115	N1	B27	C2	coupling of N1-CO-B27-OH with H-C1 and subsequent saponification with aq. NaOH	4	ESI: $(M-H)^-$ = 671; $(M+H)^+$ = 673
116	N1	B28	C2	coupling of N1-CO-B28-OH with H-C1 and subsequent saponification with aq. NaOH	4	ESI: $(M+H)^+$ = 685
117	N6	B21	C2	coupling of N6-CO-B21-OH with H-C1 and subsequent saponification with aq. NaOH	3	ESI: $(M+H)^+$ = 837/839/841 (Br_2)

Ser. no.	N	B	C	Remarks	% yield	MS
118	N1	B29	C2	coupling of N1-CO-B29-OH with H-C1 and subsequent saponification with aq. NaOH	4	ESI: $(M+H)^+$ = 699/701/703 (Cl_2)

The Examples that follow describe the preparation of pharmaceutical formulations which contain as active substance any desired compound of general formula (I):

Example I

Capsules for powder inhalation containing 1 mg of active ingredient

Composition:
1 capsule for powder inhalation contains:

active ingredient	1.0 mg
lactose	20.0 mg
hard gelatine capsules	50.0 mg
	71.0 mg

Method of preparation:
The active ingredient is ground to the particle size required for inhaled substances. The ground active ingredient is homogeneously mixed with the lactose. The mixture is transferred into hard gelatine capsules.

Example II

Inhalable solution for Respimat® containing 1 mg of active ingredient

Composition:
1 puff contains:

active ingredient	1.0 mg
benzalkonium chloride	0.002 mg
disodium edetate	0.0075 mg
purified water ad	15.0 µl

Method of preparation:
The active ingredient and benzalkonium chloride are dissolved in water and transferred into Respimat® cartridges.

Example III

Inhalable solution for nebulisers containing 1 mg of active ingredient

Composition:
1 vial contains:

active ingredient	0.1 g
sodium chloride	0.18 g
benzalkonium chloride	0.002 g
purified water ad	20.0 ml

Method of preparation:
The active ingredient, sodium chloride and benzalkonium chloride are dissolved in water.

Example IV

Propellant gas-operated metering aerosol containing 1 mg of active ingredient

Composition:

1 puff contains:	
active ingredient	1.0 mg
lecithin	0.1 %
propellant gas ad	50.0 µl

Method of preparation:

The micronised active ingredient is homogeneously suspended in the mixture of lecithin and propellant gas. The suspension is transferred into a pressurised container with a metering valve.

Example V

Nasal spray containing 1 mg of active ingredient

Composition:

active ingredient	1.0 mg
sodium chloride	0.9 mg
benzalkonium chloride	0.025 mg
disodium edetate	0.05 mg
purified water ad	0.1 ml

Method of preparation:

The active ingredient and the excipients are dissolved in water and transferred into a suitable container.

Example VI

Injectable solution containing 5 mg of active substance per 5 ml

Composition:	
active substance	5 mg
glucose	250 mg
human serum albumin	10 mg
glycofurol	250 mg
water for injections ad	5 ml

Preparation:

Glycofurol and glucose are dissolved in water for injections (Wfl); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with Wfl; transferred into ampoules under nitrogen gas.

Example VII

Injectable solution containing 100 mg of active substance per 20 ml

Composition:	
active substance	100 mg
monopotassium dihydrogen phosphate = KH_2PO_4	12 mg
disodium hydrogen phosphate = $Na_2HPO_4 \cdot 2H_2O$	2 mg
sodium chloride	180 mg
human serum albumin	50 mg
Polysorbate 80	20 mg
water for injections ad	20 ml

Preparation:

Polysorbate 80, sodium chloride, monopotassium dihydrogen phosphate and disodium hydrogen phosphate are dissolved in water for injections (Wfl); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with Wfl; transferred into ampoules.

Example VIII

Lyophilisate containing 10 mg of active substance

Composition:

Active substance	10 mg
Mannitol	300 mg
human serum albumin	20 mg

Preparation:

Mannitol is dissolved in water for injections (Wfl); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with Wfl; transferred into vials; freeze-dried.

Solvent for lyophilisate:

Polysorbate 80 = Tween 80	20 mg
mannitol	200 mg
water for injections ad	10 ml

Preparation:

Polysorbate 80 and mannitol are dissolved in water for injections (Wfl); transferred into ampoules.

Example IX

Tablets containing 20 mg of active substance

Composition:

active substance	20 mg
lactose	120 mg
maize starch	40 mg
magnesium stearate	2 mg
Povidone K 25	18 mg

Preparation:

Active substance, lactose and maize starch are homogeneously mixed; granulated with an aqueous solution of Povidone; mixed with magnesium stearate; compressed in a tablet press; weight of tablet 200 mg.

Example X

Capsules containing 20 mg active substance

Composition:

active substance	20 mg
maize starch	80 mg
highly dispersed silica	5 mg
magnesium stearate	2.5 mg

Preparation:

Active substance, maize starch and silica are homogeneously mixed; mixed with magnesium stearate; the mixture is packed into size for 3 hard gelatine capsules in a capsule filling machine.

Example XI

Suppositories containing 50 mg of active substance

Composition:	
active substance	50 mg
hard fat (Adeps solidus) q.s. ad	1700 mg

Preparation:

Hard fat is melted at about 38°C; ground active substance is homogeneously dispersed in the molten hard fat; after cooling to about 35°C it is poured into chilled moulds.

Example XII

Injectable solution containing 10 mg of active substance per 1 ml

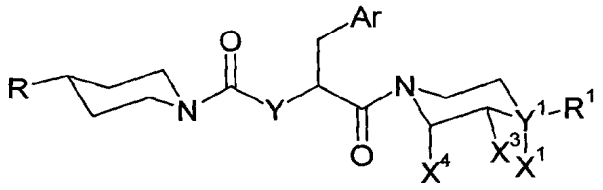
Composition:	
active substance	10 mg
mannitol	50 mg
human serum albumin	10 mg
water for injections ad	1 ml

Preparation:

Mannitol is dissolved in water for injections (Wfl); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with Wfl; transferred into ampoules under nitrogen gas.

Patent Claims

1. Carboxylic acids and esters of general formula



, (I)

wherein

R denotes a monounsaturated 5- to 7-membered diaza, triaza or *S,S*-dioxido-thiadiaza heterocycle,

while the above-mentioned heterocycles are linked via a nitrogen atom and

are characterised by a carbonyl group or sulphonyl group each flanked by two nitrogen atoms,

may be substituted at one or at two carbon atoms by an alkyl, phenyl, pyridinyl, thienyl or 1,3-thiazolyl group, while the substituents may be identical or different,

and the double bond of one of the above-mentioned unsaturated heterocycles may be fused to a benzene, pyridine or quinoline ring,

while the phenyl, pyridinyl, thienyl, or 1,3-thiazolyl groups contained in R as well as benzo-, pyrido- and quinolino-fused heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl, alkoxy, nitro, alkylthio, alkylsulphinyl, alkylsulphonyl, alkylsulphonylamino, phenyl,

trifluoromethyl, alkoxycarbonyl, carboxy, dialkylamino, hydroxy, amino, acetylamino, propionylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, methylenedioxy, aminocarbonylamino, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl groups, while the substituents may be identical or different,

Ar denotes a phenyl, 1-naphthyl, 2-naphthyl, tetrahydro-1-naphthyl, tetrahydro-2-naphthyl, 1*H*-indol-3-yl, 1-methyl-1*H*-indol-3-yl, 1-formyl-1*H*-indol-3-yl, 4-imidazolyl, 1-methyl-4-imidazolyl, 2-thienyl, 3-thienyl, thiazolyl, 1*H*-indazol-3-yl, 1-methyl-1*H*-indazol-3-yl, benzo[b]furyl, 2,3-dihydrobenzo[b]furyl, benzo[b]thienyl, pyridinyl, quinolinyl or isoquinolinyl group,

while the above-mentioned aromatic and heteroaromatic groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, by alkyl groups, C_{3-8}-cycloalkyl groups, phenylalkyl groups, alkenyl, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonyl, carboxy, dialkylamino, nitro, hydroxy, amino, alkylamino, acetylamino, propionylamino, methylsulphonyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkanoyl, cyano, trifluoromethoxy, trifluoromethylthio, trifluoromethyl-sulphinyl or trifluoromethylsulphonyl groups and the substituents may be identical or different,

Y denotes the methylene or the -NH- group,

Y^1 denotes the carbon or the nitrogen atom,

X^1 denotes the pair of free electrons, if Y^1 denotes the nitrogen atom, or, if Y^1 is the carbon atom, denotes a hydrogen atom or a carboxylic acid group optionally esterified with a lower aliphatic alcohol,

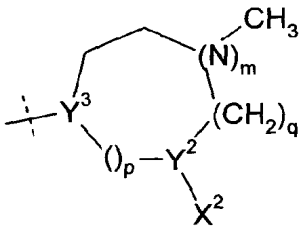
X^3 and X^4 in each case denote the hydrogen atom or the carboxylic acid

group optionally esterified with a lower aliphatic alcohol,

with the proviso that at least one but also not more than one of the groups X^1, X^2, X^3 or X^4 contains an optionally esterified carboxylic acid function,

and

R^1 denotes a group of general formula



, (IIa)

wherein

Y^2 denotes the carbon or, if m assumes the value 0, also the nitrogen atom,

Y^3, which is always different from Y^1, denotes the carbon or nitrogen atom,

X^2 denotes a group of general formula

$$CH_2CO_2R^2 \quad , (III)$$

wherein

R^2 denotes the hydrogen atom or a C_{1-5}-alkyl group,

or, if Y^2 is the carbon atom, it may also denote the hydrogen atom or the carboxylic acid group optionally esterified with a lower aliphatic alcohol,

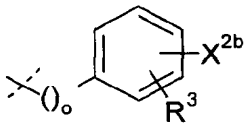
m denotes the numbers 0 or 1,

p denotes the numbers 0, 1, 2 or 3 and

q denotes the numbers 0, 1 or 2,

while the sum of m, p and q may assume the values 1, 2 or 3,

or one of the groups (IIb), (IIc) or (IId)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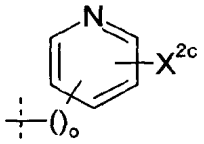
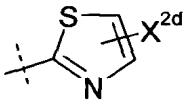

(IIc), or

, (IId)

wherein

X^{2b}, X^{2c} and X^{2d} each denote the hydrogen atom or a carboxylic acid group optionally esterified with a lower aliphatic alcohol,

o denotes the numbers 0, 1, 2 or 3 and

R^3 denotes the hydrogen atom, the fluorine, chlorine or bromine atom, an alkyl, alkoxy, nitro, trifluoromethyl, hydroxy, amino, acetylamino, aminocarbonyl, acetyl or cyano group,

while, unless otherwise stated, the above-mentioned alkyl groups or the alkyl groups contained in the above-mentioned groups contain 1 to 5 carbon atoms and may be straight-chain or branched,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and

the salts thereof.

2. Carboxylic acids and esters of general formula I according to claim 1, wherein

R denotes a monounsaturated 5- to 7-membered diaza, triaza or *S,S*-dioxido-thiadiaza heterocycle,

while the above-mentioned heterocycles are linked via a nitrogen atom and

are characterised by a carbonyl group or sulphonyl group in each case flanked by two nitrogen atoms,

may be substituted at a carbon atom by a phenyl, pyridinyl, thienyl or 1,3-thiazolyl group,

and the double bond of one of the above-mentioned unsaturated heterocycles may be fused to a benzene, pyridine or quinoline ring,

while the phenyl, pyridinyl, thienyl, or 1,3-thiazolyl groups contained in R as well as benzo-, pyrido- and quinolino-fused heterocycles in the carbon skeleton may additionally be mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms, by alkyl, alkoxy, trifluoromethyl, amino, cyano or acetylamino groups, while the substituents may be identical or different,

Ar denotes a phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl or 2,3-dihydrobenzo[b]fur-5-yl group,

while the above-mentioned aromatic and heteroaromatic groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, by alkyl groups, alkoxy, trifluoromethyl, nitro, hydroxy, amino, aminocarbonyl, acetyl or cyano

groups and the substituents may be identical or different,

Y denotes the methylene or the -NH- group,

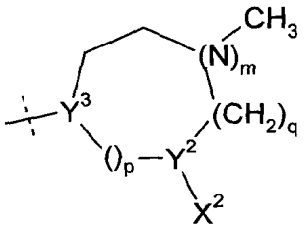
Y^1 denotes the carbon or the nitrogen atom,

X^1 denotes a pair of free electrons, if Y^1 denotes the nitrogen atom, or, if Y^1 is the carbon atom, the hydrogen atom or the carboxylic acid group optionally esterified with a lower aliphatic alcohol,

X^3 and X^4 each denote the hydrogen atom or the carboxylic acid group optionally esterified with a lower aliphatic alcohol,

with the proviso that at least one but also not more than one of the groups X^1, X^2, X^3 or X^4 contains an optionally esterified carboxylic acid function, and

R^1 denotes a group of general formula



, (IIa)

wherein

Y^2 denotes the carbon atom or, if m assumes the value 0, may also denote the nitrogen atom,

Y^3, which is always different from Y^1, denotes the carbon or the nitrogen atom,

X^2 denotes a group of general formula

$CH_2CO_2R^2$, (III)

wherein

R^2 denotes the hydrogen atom or a C_{1-5}-alkyl group,

or, if Y^2 is the carbon atom, also denotes the hydrogen atom or the carboxylic acid group optionally esterified with a lower aliphatic alcohol,

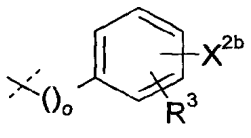
m denotes the numbers 0 or 1,

p denotes the numbers 0, 1 or 2 and

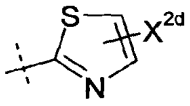
q denotes the numbers 0, 1 or 2,

while the sum of m, p and q may assume the values 1 or 2,

or one of the groups



(IIb), or



, (IId)

wherein

X^{2b} and X^{2d} each denote the hydrogen atom or the carboxylic acid group optionally esterified with a lower aliphatic alcohol,

o denotes the numbers 0, 1, 2 or 3 and

R^3 denotes the hydrogen atom, the fluorine, chlorine or bromine atom, a methyl, methoxy, nitro, trifluoromethyl or cyano group,

while, unless otherwise stated, the above-mentioned alkyl groups or the alkyl groups contained in the above-mentioned groups contain 1 to 4 carbon atoms and may be branched or unbranched,

the tautomers, the diastereomers, the enantiomers and the salts thereof.

3. Carboxylic acids and esters of general formula I according to claim 1, wherein

R denotes a monounsaturated 5- to 7-membered diaza, triaza or *S,S*-dioxido-thiadiaza heterocycle,

while the above-mentioned heterocycles are linked via a nitrogen atom and

are characterised by a carbonyl group or sulphonyl group each flanked by two nitrogen atoms,

may be substituted at a carbon atom by a phenyl group,

and the double bond of one of the above-mentioned unsaturated heterocycles may be fused to a benzene, pyridine or quinoline ring,

while the phenyl groups contained in R as well as benzo-, pyrido- and quinolino-fused heterocycles may additionally be mono- or disubstituted in the carbon skeleton by fluorine, chlorine or bromine atoms, by methyl, methoxy, trifluoromethyl, or cyano groups, while the substituents may be identical or different,

Ar denotes a phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl or 2,3-dihydrobenzo[b]fur-5-yl group,

while the above-mentioned aromatic and heteroaromatic groups may additionally be mono-, di- or trisubstituted in the carbon skeleton by

fluorine, chlorine or bromine atoms, by methyl, methoxy, trifluoromethyl, hydroxy or amino groups and the substituents may be identical or different,

Y denotes the methylene or -NH- group,

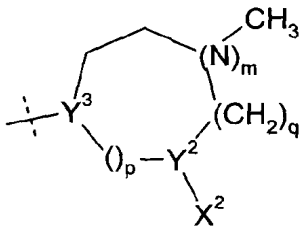
Y^1 denotes the carbon or nitrogen atom,

X^1 denotes a pair of free electrons, if Y^1 denotes the nitrogen atom, or, if Y^1 is the carbon atom, the hydrogen atom or the carboxylic acid group optionally esterified with methanol or ethanol,

X^3 and X^4 each denote the hydrogen atom or the carboxylic acid group optionally esterified with methanol or ethanol,

with the proviso that at least one but also not more than one of the groups X^1, X^2, X^3 or X^4 contains an optionally esterified carboxylic acid function, and

R^1 denotes a group of general formula



, (IIa)

wherein

Y^2 denotes the carbon or, if m assumes the value 0, also denotes the nitrogen atom,

Y^3, which is always different from Y^1, denotes the carbon or the nitrogen atom,

X^2 denotes a group of general formula

$$CH_2CO_2R^2 \quad , (III)$$

wherein

R^2 denotes the hydrogen atom or a straight-chain or branched C_{1-4}-alkyl group,

or, if Y^2 is the carbon atom, also denotes the hydrogen atom or the carboxylic acid group optionally esterified with methanol or ethanol,

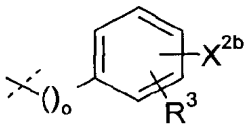
m denotes the numbers 0 or 1,

p denotes the numbers 0, 1 or 2 and

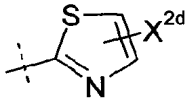
q denotes the numbers 0, 1 or 2,

while the sum of m, p and q may assume the values 1 or 2,

or one of the groups



(IIb), or



, (IId)

wherein

X^{2b} and X^{2d} each denote the hydrogen atom or the carboxylic acid group optionally esterified with methanol or ethanol,

o denotes the numbers 0, 1 or 2 and

R^3 denotes the hydrogen atom, the fluorine, chlorine or bromine atom, a methyl, methoxy or trifluoromethyl group,

while, unless otherwise stated, the above-mentioned alkyl groups or the alkyl groups contained in the above-mentioned groups contain 1 to 4 carbon atoms and may be straight-chain or branched,

the tautomers, the diastereomers, the enantiomers and the salts thereof.

4. Carboxylic acids and esters of general formula I according to claim 1, wherein

R denotes the 3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl, 2,4-dihydro-5-phenyl-3(3*H*)-oxo-1,2,4-triazol-2-yl, 1,3-dihydro-2(2*H*)-oxoimidazo[4,5-c]quinolin-3-yl, 2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl, 3,4-dihydro-2(1*H*)-oxopyrido[3,4-d]pyrimidin-3-yl or 3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl group,

Ar denotes the 3,5-dibromo-4-hydroxyphenyl, 4-amino-3,5-dibromophenyl, 4-bromo-3,5-dimethylphenyl, 3,5-dichloro-4-methylphenyl, 3,4-dibromophenyl, 3-bromo-4,5-dimethylphenyl, 3,5-dibromo-4-methylphenyl, 3-chloro-4-methylphenyl, 3,4-difluorophenyl, 4-hydroxyphenyl, 1-naphthyl, 3,5-dibromo-4-fluorophenyl, 3,5-bis-(trifluoromethyl)-phenyl, 3,4,5-trimethylphenyl, 3-(trifluoromethyl)-phenyl, 3,5-dimethyl-4-methoxyphenyl, 4-amino-3,5-dichlorophenyl, 2,4-bis-(trifluoromethyl)-phenyl, 3,4,5-tribromophenyl, 3,4-dimethoxyphenyl, 3,4-dichlorophenyl, 4-bromo-3,5-dichlorophenyl, 2-naphthyl, 2,3-dihydrobenzo[b]fur-5-yl, 1,2,3,4-tetrahydro-1-naphthyl or 2,3-dichlorophenyl group,

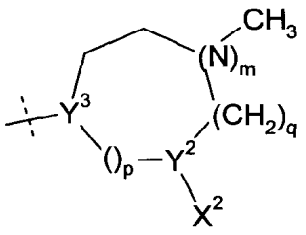
Y denotes the methylene or the -NH- group,

Y^1 denotes the carbon or the nitrogen atom,

X^1 denotes a pair of free electrons, if Y^1 denotes the nitrogen atom, or, if Y^1 is

the carbon atom, the hydrogen atom, the carboxylic acid or the methoxy-carbonyl group and

R^1 denotes a group of general formula



, (IIa)

wherein

Y^2 denotes the carbon atom or, if m assumes the value 0, also the nitrogen atom,

Y^3, which is always different from Y^1, denotes the carbon or the nitrogen atom,

X^2 denotes a group of general formula

$$CH_2CO_2R^2 \quad , (III)$$

wherein

R^2 denotes the hydrogen atom or a straight-chain or branched C_{1-4}-alkyl group,

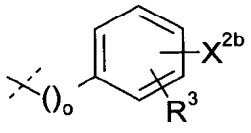
or, if Y^2 is the carbon atom, also denotes the hydrogen atom or the carboxylic acid group optionally esterified with methanol or ethanol,

m denotes the numbers 0 or 1,

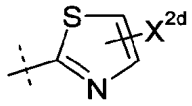
p and q in each case denotes the numbers 0, 1 or 2,

while the sum of m, p and q may assume the values 1 or 2,

or one of the groups


(IIb),

or


, (IId)

wherein

X^{2b} denotes the hydrogen atom or the carboxylic acid group optionally esterified with methanol or ethanol,

X^{2d} denotes the hydrogen atom or the carboxylic acid group optionally esterified with methanol,

o denotes the numbers 0, 1 or 2 and

R^3 denotes the hydrogen atom or the trifluoromethyl group,

while, unless otherwise stated, the above-mentioned alkyl groups or the alkyl groups contained in the above-mentioned groups contain 1 to 4 carbon atoms and may be straight-chain or branched,

the tautomers, the diastereomers, the enantiomers and the salts thereof.

5. The following carboxylic acids and esters of general formula I according to claim 1:

(1) ethyl 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-1-piperazineacetate,

(2) 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-1-piperazineacetic acid,

(3) 1,1-dimethylethyl 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-1-piperidineacetate,

(4) 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-1-piperidineacetic acid,

(5) methyl 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-[1,4']bipiperidinyl-4-acetate,

(6) 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-[1,4']bipiperidinyl-4-acetic acid,

(7) ethyl *endo*-4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-cyclohexanecarboxylate,

(8) *endo*-4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-cyclohexanecarboxylic acid,

(9) ethyl *exo*-4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-cyclohexanecarboxylate,

(10) *exo*-4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-cyclohexanecarboxylic acid,

(11) ethyl 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-1-piperidineacetate,

(12) methyl 1'-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-[1,4']bipiperidinyl-4-acetate,

(13) 1'-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-[1,4']bipiperidinyl-4-acetic acid,

(14) ethyl 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-1-piperidineacetate,

(15) ethyl 4-{1-[4-bromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3,5-dimethyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(16) ethyl 4-{1-[3,5-dichloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(17) ethyl 4-{1-[3,4-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(18) ethyl 4-{1-[3-bromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4,5-dimethyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(19) ethyl 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(20) ethyl 4-{1-[3-chloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-

piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(21) ethyl 4-{4-[4-bromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3,5-dimethyl-D,L-phenylalanyl]-1-piperazinyl}-1-piperidineacetate,

(22) 4-{1-[4-bromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3,5-dimethyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(23) 4-{1-[3,5-dichloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(24) 4-{1-[3,4-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(25) 4-{1-[3-bromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4,5-dimethyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(26) 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(27) 4-{1-[3-chloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(28) 4-{4-[4-bromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-3,5-dimethyl-D,L-phenylalanyl]-1-piperazinyl}-1-piperidineacetic acid,

(29) 1,1-dimethylethyl 4-{1-[3,4-difluoro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D,L-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(30) methyl 1'-[*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-[1,4']bipiperidinyl-4-acetate,

(31) ethyl 4-{1-[*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-1-piperazineacetate,

(32) ethyl (*R*,*S*)-4-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetate,

(33) methyl 1-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-(*S*)-pyrrolidine-2-carboxylate,

(34) methyl 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-(*S*)-pyrrolidine-2-carboxylate,

(35) 1-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-(*S*)-pyrrolidine-2-carboxylic acid,

(36) 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-(*S*)-pyrrolidine-2-carboxylic acid,

(37) methyl 1-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-(*R*)-pyrrolidine-2-carboxylate,

(38) methyl 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-(*R*)-pyrrolidine-2-carboxylate,

(39) 1-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-(*R*)-pyrrolidine-2-carboxylic acid,

(40) 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-(*R*)-pyrrolidine-2-carboxylic acid,

(41) methyl 1'-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-(*R*)-[1,4']bipiperidinyl-2-carboxylate,

(42) methyl 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-(*R*)-[1,4']bipiperidinyl-2-carboxylate,

(43) methyl 1'-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-(*S*)-[1,4']bipiperidinyl-2-carboxylate,

(44) methyl 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-(*S*)-[1,4']bipiperidinyl-2-carboxylate,

(45) 1'-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-(*R*)-[1,4']bipiperidinyl-2-carboxylic acid,

(46) 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-(*R*)-[1,4']bipiperidinyl-2-carboxylic acid,

(47) 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-(*S*)-[1,4']bipiperidinyl-2-carboxylic acid,

(48) 1'-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-(*S*)-[1,4']bipiperidinyl-2-carboxylic acid,

(49) methyl 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-[1,4']bipiperidinyl-4'-carboxylate,

(50) methyl 1'-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-[1,4']bipiperidinyl-4'-carboxylate,

(51) 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-[1,4']bipiperidinyl-4'-carboxylic acid,

(52) 1'-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-[1,4']bipiperidinyl-4'-carboxylic acid,

(53) 1'-[*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-[1,4']bipiperidinyl-4-acetic acid,

(54) 4-{1-[*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-1-piperazineacetic acid,

(55) ethyl 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-benzoate,

(56) ethyl 3-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-benzoate,

(57) methyl 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-

1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-benzoate,

(58) ethyl 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinylmethyl}-benzoate,

(59) ethyl 4-{2-[1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl]-ethyl}-benzoate,

(60) methyl 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-3-(trifluoromethyl)-benzoate,

(61) methyl 3-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-benzoate,

(62) ethyl 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-benzoate,

(63) ethyl 3-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-benzoate,

(64) methyl 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-benzoate,

(65) methyl 4-{2-[1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl]-ethyl}-benzoate,

(66) methyl 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-3-(trifluoromethyl)-benzoate,

(67) methyl 3-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-benzoate,

(68) 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-benzoic acid,

(69) 3-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-benzoic acid,

(70) 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-benzoic acid,

(71) 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinylmethyl}-benzoic acid,

(72) 4-{2-[1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl]-ethyl}-benzoic acid,

(73) 4-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-3-(trifluoromethyl)-benzoic acid,

(74) 3-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-piperidinyl}-benzoic acid,

(75) 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-benzoic acid,

(76) 3-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-benzoic acid,

(77) 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-terahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-benzoic acid,

(78) 4-{2-[1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl]-ethyl}-benzoic acid,

(79) 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-3-(trifluoromethyl)-benzoic acid,

(80) 3-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-benzoic acid,

(81) ethyl 4-{1-[3-(1-naphthyl)-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-alanyl]-4-piperidinyl}-1-piperazineacetate,

(82) 4-{1-[3-(1-naphthyl)-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-alanyl]-4-piperidinyl}-1-piperazineacetic acid,

(83) methyl 2-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-5-thiazolecarboxylate,

(84) methyl 2-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-4-thiazolecarboxylate,

(85) 2-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-5-thiazolecarboxylic acid,

(86) 2-{4-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-1-piperazinyl}-4-thiazolecarboxylic acid,

(87) methyl 2-{4-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-4-thiazolecarboxylate,

(88) methyl 2-{4-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-5-thiazolecarboxylate,

(89) 2-{4-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-4-thiazolecarboxylic acid,

(90) 2-{4-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-5-thiazolecarboxylic acid,

(91) 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-1-piperidineacetic acid,

(92) 4-{4-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-1-piperazinyl}-1-piperidineacetic acid,

(93) 1,1-dimethylethyl 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(94) 1,1-dimethylethyl 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(95) ethyl 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(96) ethyl 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-1-piperazineacetate,

(97) 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(98) 4-{1-[4-amino-3,5-dibromo-*N*-[[4-(2-oxo-1,3,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-piperidinyl}-1-piperazineacetic acid,

(99) (*R,S*)-4-{1-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(100) (*R,S*)-4-{1-[2-[(3,5-dibromo-4-fluorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(101) (*R,S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxopyrido[3,4-d]pyrimidin-3-yl)-1-piperidinyl]-2-[(1-naphthyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(102) (*R,S*)-4-{1-[2-[[3,5-bis-(trifluoromethyl)-phenyl]methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(103) (*R,S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-

[(3,4,5-trimethylphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(104) (*R,S*)-4-{1-[2-[(3-bromo-4,5-dimethylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(105) (*R,S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[[3-(trifluoromethyl)-phenyl]methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(106) (*R,S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-methoxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(107) (*R,S*)-4-{1-[2-[(4-amino-3,5-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(108) (*R,S*)-4-{1-[2-[[2,4-bis-(trifluoromethyl)-phenyl]methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(109) (*R,S*)-4-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(110) (*R,S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4,5-tribromophenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(111) (*R,S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dimethoxyphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(112) (*R*,*S*)-4-{1-[2-[(3,4-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(113) (*R*,*S*)-4-{1-[2-[(4-bromo-3,5-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(114) (*R*,*S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(2-naphthyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(115) (*R*,*S*)-4-{1-[2-[(2,3-dihydrobenzo[b]fur-5-yl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(116) (*R*,*S*)-4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(1,2,3,4-tetrahydro-1-naphthyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(117) (*R*,*S*)-4-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(118) (*R*,*S*)-4-{1-[2-[(2,3-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(119) ethyl (*R*,*S*)-4-{1-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetate,

(120) (*R*,*S*)-4-{1-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-

oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-piperazineacetic acid,

(121) (*R,S*)-4-{4-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-piperazinyl}-1-piperidineacetic acid,

(122) methyl 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-(*S*)-pyrrolidine-2-carboxylate,

(123) methyl 1-{1-[3-chloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-(S)-pyrrolidine-2-carboxylate,

(124) methyl 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-(*R*)-pyrrolidine-2-carboxylate,

(125) methyl 1-{1-[3-chloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-(*R*)-pyrrolidine-2-carboxylate,

(126) 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-(S)-pyrrolidine-2-carboxylic acid,

(127) 1-{1-[3-chloro-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-(*S*)-pyrrolidine-2-carboxylic acid,

(128) ethyl 4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethyl-4-hydroxyphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(129) ethyl 4-{1-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(130) ethyl 4-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylate,

(131) ethyl 4-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(132) ethyl 4-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylate,

(133) ethyl 4-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylate,

(134) 4-{1-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylic acid,

(135) 4-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylic acid,

(136) 4-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylic acid,

(137) 4-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-

oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylic acid,

(138) ethyl 4-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylate,

(139) 4-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylic acid,

(140) ethyl 4-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylate,

(141) ethyl 4-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylate,

(142) ethyl 4-{1-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(143) 4-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylic acid,

(144) 4-{1-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylic acid,

(145) 4-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylic acid,

(146) 4-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylic acid,

(147) ethyl 4-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethyl-4-hydroxyphenyl)methyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-2-piperazinecarboxylate,

(148) ethyl 4-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethyl-4-hydroxyphenyl)methyl]-1,4-dioxobutyl]-1-(1-methyl-4-piperidinyl)-3-piperazinecarboxylate,

(149) 4-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethyl-4-hydroxyphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylic acid,

(150) ethyl 4-{1-[2-[(4-bromo-3,5-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(151) ethyl 1-{1-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylate,

(152) ethyl 1-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylate,

(153) ethyl 1-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethyl-4-hydroxyphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylate,

(154) ethyl 1-{1-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-

2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylate,

(155) ethyl 1-{1-[2-[(4-bromo-3,5-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylate,

(156) 1-{1-[2-[(3,5-dibromo-4-methylphenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylic acid,

(157) 1-{1-[4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dimethyl-4-hydroxyphenyl)methyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylic acid,

(158) 1-{1-[2-[(4-amino-3,5-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylic acid,

(159) 1-{1-[2-[(4-bromo-3,5-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylic acid,

(160) 1-{1-[2-[(3,4-dibromophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylic acid,

(161) ethyl 4-{1-[3,4-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-phenylalanyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(162) 4-{1-[2-[(4-bromo-3,5-dichlorophenyl)methyl]-4-[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]-1,4-dioxobutyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylic acid,

(163) methyl 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-phenylalanyl]-[1,4']bipiperidinyl-4-acetate,

(164) 1'-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-phenylalanyl]-[1,4']bipiperidinyl-4-acetic acid,

(165) ethyl 4-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-1-methyl-2-piperazinecarboxylate,

(166) ethyl 1-{1-[3,5-dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-4-methyl-D,L-phenylalanyl]-4-piperidinyl}-4-methyl-2-piperazinecarboxylate

and the salts thereof.

6. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 5 with inorganic or organic acids or bases inorganic or organic acids or bases.

7. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 5 or a physiologically acceptable salt according to claim 6 optionally together with one or more inert carriers and/or diluents.

8. Use of a compound according to at least one of claims 1 to 6 for preparing a pharmaceutical composition for the acute or prophylactic treatment of headaches, for treating non-insulin-dependent diabetes mellitus, cardiovascular diseases, morphine tolerance, skin diseases, inflammatory diseases, allergic rhinitis, asthma, diseases accompanied by excessive vasodilatation and resultant reduced circulation of the blood, for acute or preventive treatment of the menopausal hot flushes in oestrogen-deficient women or for treating pain.

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